약학석사학위논문

Synthesis of Homoaristeromycin Analogues as Potent Antiviral Agents

강력한 항바이러스제로서의 Homoaristeromycin 유사체의 합성

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Abstract

(–)-Aristeromycin (**1**) exhibits significant antiviral activity through inhibition of *S*-adenosylhomocysteine (SAH) hydrolase, which has been a promising target for many broad antiviral agents. However, its therapeutic utility has been limited due to its the significant toxicity. This cytotoxicity arise from 5′-phosphorylation to the corresponding nucleotides by cellular kinase. To lower cytotoxicity, an approach of extending the C-5′ hydroxymethyl side chain by one carbon homologation was made to provide the C-5′ homolog of (–)-aristeromycin. Furthermore, we thought that introduction of fluorine atom at 6′-position which is bioisostere with hydrogen atom improves antiviral activity by SAH hydrolase inhibitory effect.

Based on these strategy, 6′-fluoro-homoaristeromycin analogues were designed and synthesized via Michael reaction and stereoselective electrophilic fluorination as key steps. (–)-6′-*β*-Fluoro-homoaristeromycin (**3**) showed potent inhibition of SAH hydrolase (IC_{50} = 0.36 nM), high anti-Chikungunya activity (EC_{50} = 0.12 μM) and low cytotoxicity (CC_{50} > 250 μM). Selectivity index is more than 2087.

In brief, the (–)-6′-*β*-fluoro-homoaristeromycin (**3**) showed potent activity against Chikungunya virus and low toxicity. This study can be extensively applied to the development of potent antiviral agents.

Keywords : Antiviral, Aristeromycin, Carbocyclic nucleoside, Fluorination, Chikungunya virus

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Contents

I. Introduction

Nucleosides are fundamental elements in all living systems and building blocks of nucleic acids. Modified nucleosides have been playing major role in fighting tumors and viruses, either as selective inhibitors of certain necessary enzymes for cancer or viral reproduction or as nucleic acid chain terminators that interrupt the replication of cancer cells or a virus.[1]

The carbocyclic nucleosides, in which the furanose oxygen has been replaced by methylene group, have the inherent strength that they are not subject to the action of nucleoside phosphorylases and hydrolases that cleave normal nucleosides.[2]

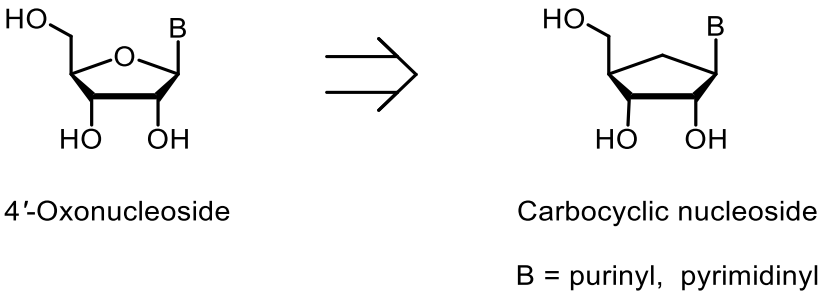
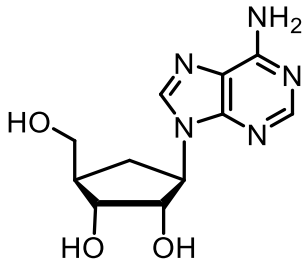


Figure 1. Gradual evolution of a nucleoside.

The adenosine analogue, (−)-aristeromycin is isolated from *Streptomyces citricolor* and the representative of naturally occurring carbocyclic nucleosides. (−)-Aristeromycin exhibits both significant antiviral and antitumor activity.[3,4]

This compound shows as potent activity against *S*-adenosylhomocysteine (SAH) hydrolase, which is an enzyme responsible for the hydrolysis of *S*-adenosylhomocysteine (SAH) into adenosine and L-homocysteine. SAH is a strong feedback inhibitor of a methyltransferase enzyme that involves *S*-adenosyl-L-methionine (SAM), which results in inhibition of biological methylation of viral RNA. Therefore, inhibition of SAH hydrolase represents a rational strategy for development of antiviral chemotherapy.[5,6]



1
(–)-Aristeromycin

Figure 2. Structure of (–)-aristeromycin (1)

As a number of viruses are sensitive to SAH hydrolase inhibitors, the inhibitors show a broad antiviral activity spectrum. Members of the *Poxviridae* and *Rhabdoviridae* are exquisitely sensitive to SAH hydrolase inhibitors. In addition, SAH hydrolase inhibitors were shown to be effective against human immunodeficiency virus (HIV) but only under specific test conditions (optimized for minimizing cytotoxicity). However, the (+)-RNA viruses other than retroviruses (HIV) are virtually insensitive to SAH hydrolase inhibitors.[6]

Thus, SAH hydrolase has been recognized for a long time as a potential target for antiviral chemotherapy and several carbocyclic nucleosides[7] were found to exert their antiviral action through inhibition of SAH hydrolase.

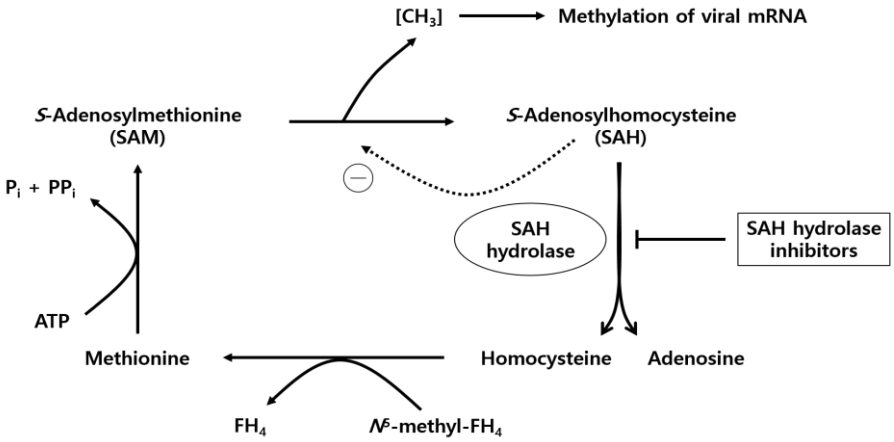


Figure 3. The mechanism of action of SAH hydrolase inhibitors.[7]

Though (−)-aristeromycin is a potent SAH hydrolase inhibitor, its therapeutic utility has been limited, because of the significant toxicity. This cytotoxicity arise from through 5′-phosphorylation of the corresponding nucleotides by cellular kinase. Therefore, modifications based on (−)-aristeromycin have generated a series of carbocyclic analogues that retain the inhibitory activity toward SAH hydrolase, while being devoid of the toxicity.[4]

Our group designed fluorinated homoaristeromycin to lower cytotoxicity and improve activity against viruses. First of all, an approach is extension of the C-5′ hydroxymethyl side chain by one carbon homologation to provide the C-5′ homolog of (−)-aristeromycin. This analog can be expected to have displaced the phosphate-susceptible hydroxyl from the phosphate-transfer zone in the kinases. In support of this, (−)-homoaristeromycin **2** has been reported to be inactive against HSV-1 and HSV-2, possibly, due to its failure to be phosphorylated.[8] Furthermore, we thought that introduction of fluorine which is bioisostere with hydrogen atom improves activity against SAH hydrolase and viruses.

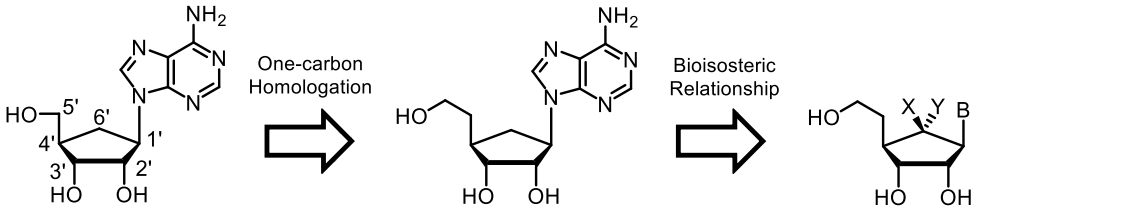
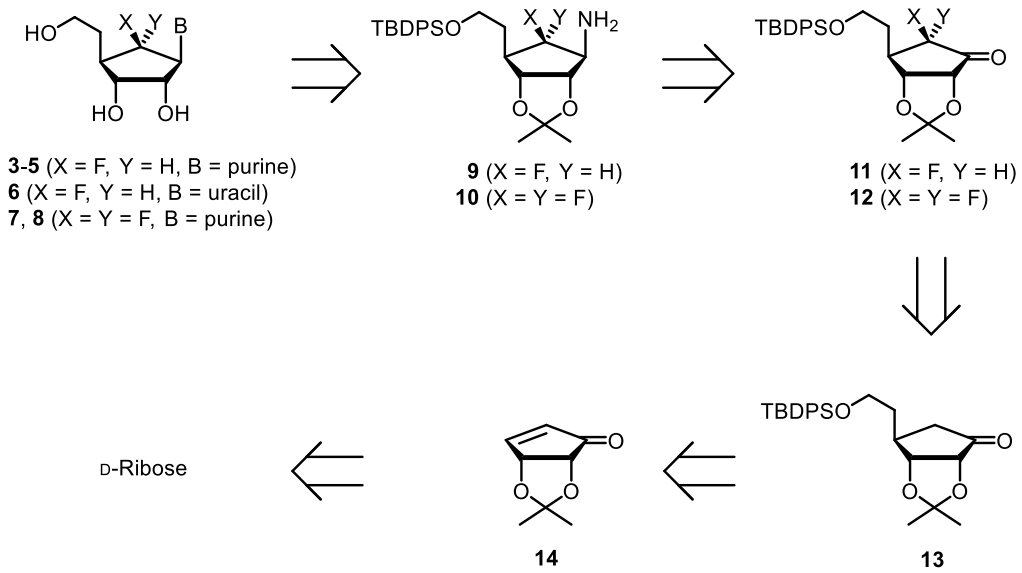


Figure 4. Rationale for the design of the fluorinated homoaristeromycin analogues.

Herein, we designed and synthesized enantiomerically pure 6′-fluoroaristeromycin. We envisaged that we could stereoselective synthesize and examine the biological activities for the fluorinated aristeromycin analogues. This could be achieved from an inexpensive starting material like D-ribose.

II. Results and Discussion

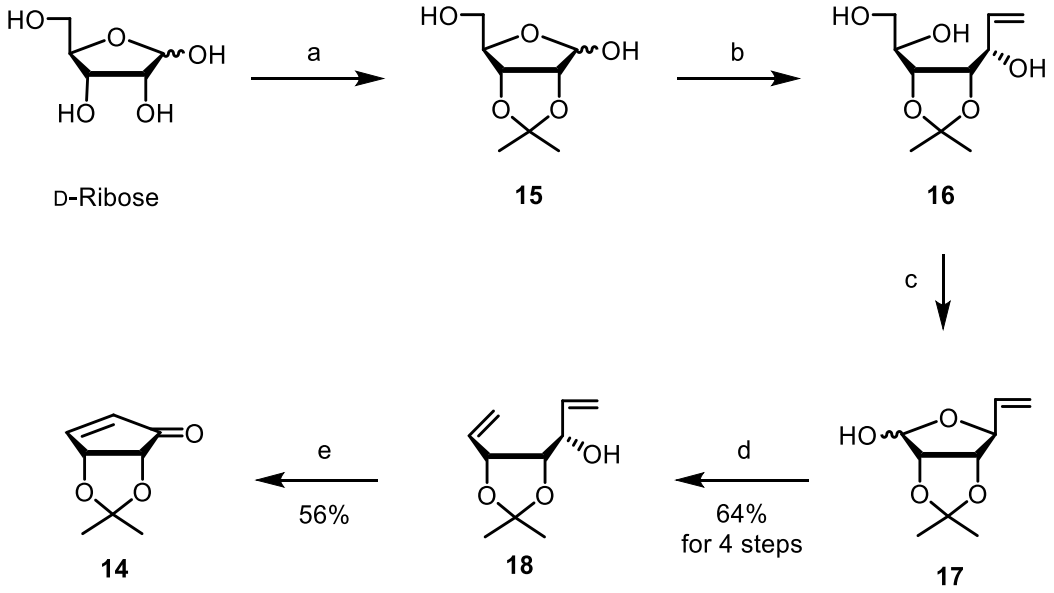
For many years, our laboratory has researched for our continuing interest in the development of several types of carbocyclic nucleosides.[10,11] Therefore, we have gained substantial insights toward the synthesis of glycosyl donors from a relatively inexpensive and chiral starting material D-ribose.



Scheme 1. Retrosynthetic analysis of the fluorinated homoaristeromycin analogues.

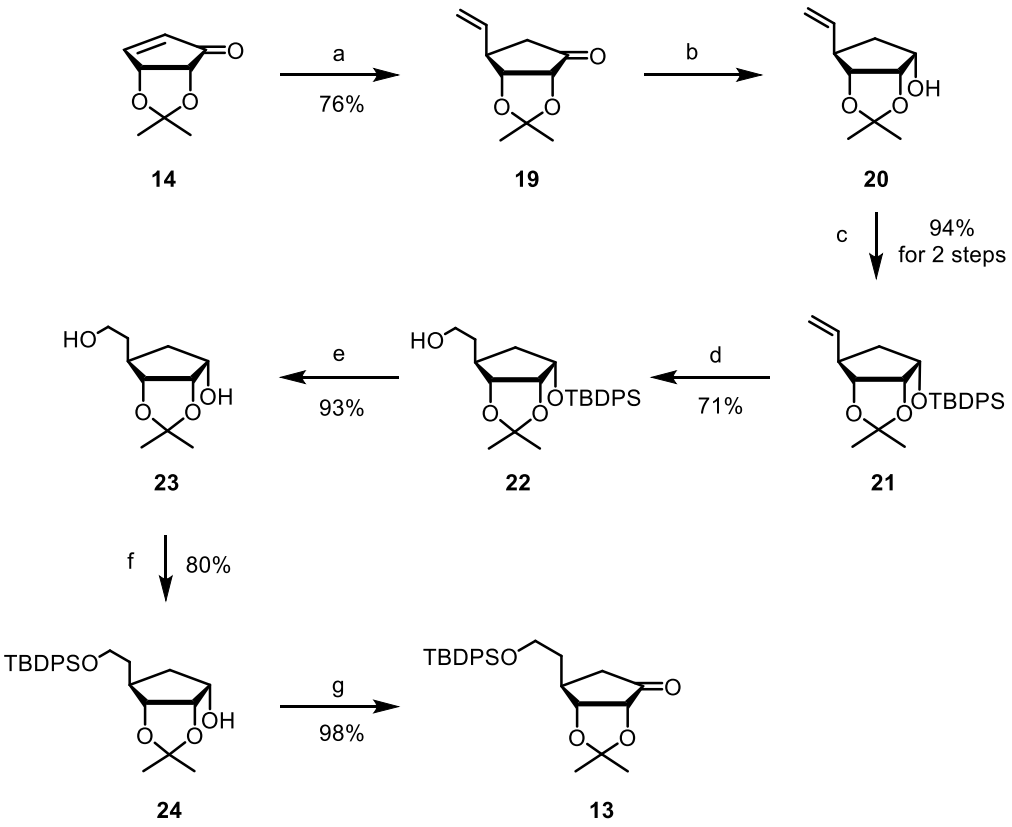
As shown in our retrosynthetic plans (Scheme 1), our strategy would utilize the linear purine and pyrimidine base build-up approach from amino intermediate **9** and **10**, which could easily be derived from **11** and **12**. It was envisaged that the *β*-fluoroketone **11** could be synthesized through a stereoselective electrophilic fluorination of silyl enol ether, which could be easily accessed from compound **13**. Di-fluorinated compound **12** could be also synthesized through same procedure from the *β*-fluoroketone **11**. Compound **19** could be synthesized from D-cyclopentenone **14** by a Michael reaction and the intermediate **14** could be efficiently derived from D-ribose with our previously published procedure[12].

To begin our synthesis (Scheme 2), D-ribose was converted to known **14** in five steps, according to a modified known procedure[12] using ring-closing metathesis of **18** with Neolyst M2, followed by PDC oxidation.



Reagents and conditions: (a) acetone, *c*-H_2SO_4, rt, 3 h; (b) vinylMgBr, THF, –78 °C to 0 °C, 3 h; (c) $NaIO_4$, H_2O, 0 °C to rt, 40 min; d) NaH, DMSO, CH_3PPh_3Br, THF, 0 °C to reflux, 15 h; (e) (i) Neolyst M2, CH_2Cl_2, rt, 2 d; (ii) PDC, CH_2Cl_2, rt, 6 h.

Scheme 2. Synthesis of D-cyclopentenone **14**.

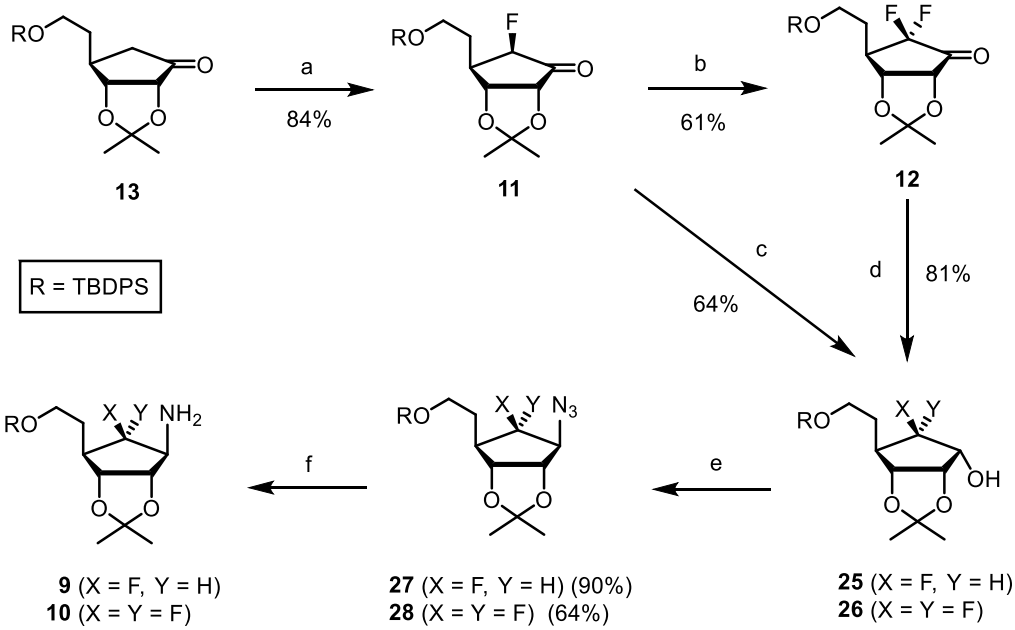


Reagent and Conditions: (a) vinylMgBr, $CuBr{\cdot}CH_3SCH_3$, TMSCl, HMPA, THF, –78 °C, 2 h; (b) $NaBH_4$, MeOH, 0 °C, 1 h; (c) TBDPSCl, imidazole, DMF, 0 °C to rt, 3 h; (d) (i) $BH_3{\cdot}CH_3SCH_3$, THF, 0 °C to rt, 1 h; (ii) $NaBO_3{\cdot}H_2O$, H_2O, 0 °C to rt, 16 h; (e) TBAF, THF, 0 °C to rt, 16 h; (f) Et_3N, DMAP, TBDPSCl (1.2 eq.), CH_2Cl_2, 0 °C to rt, 2 h; (g) NMO, 4 Å molecular sieves, TPAP, CH_2Cl_2, rt, 1 h.

Scheme 3. Synthesis of the ketone intermediate **13**.

Michael addition of vinyl Grignard on **14** afforded known compound **19**[13] in 76% yield. The reduction of 1,4-addition product **19** using sodium borohydride gave the alpha alcohol **20**, since the concave region is hindered by the 2,3-isopropylidene ring group. The alcohol **20** was protected with TBDPSCl, followed by hydroboration oxidation with borane-dimethyl sulfide complex to give the hydroboration product **22**. The deprotection of TBDPS using TBAF gave the diol compound **23**, which was subjected to selective

protection of primary hydroxyl group by 1.2 equivalent of TBDPSCl to afford compound **24**. The oxidation of compound **24** in the presence of tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide gave the ketone **13**.



Reagent and Conditions: (a) (i) TESCl, LiHMDS, THF, –78 °C, 1 h; (ii) selectfluor, CH_3CN, 0 °C, 16 h; (b) (i) TESCl, LiHMDS, THF, –78 °C, 1 h; (ii) selectfluor, CH_3CN, 0 °C, 16 h; (c) $NaBH_4$, THF, –40 °C to 0 °C, 3 h; (d) $NaBH_4$, THF, 0 °C, 3 h; (e) (i) Tf_2O, pyridine, 0 °C, 1 h; (ii) NaN_3, DMF, 100 °C (for **27**) or 60 °C (for **28**), 12 h; (f) H_2, Pd/C, MeOH, rt, 3 h (for **9**) or 12 h (for **10**).

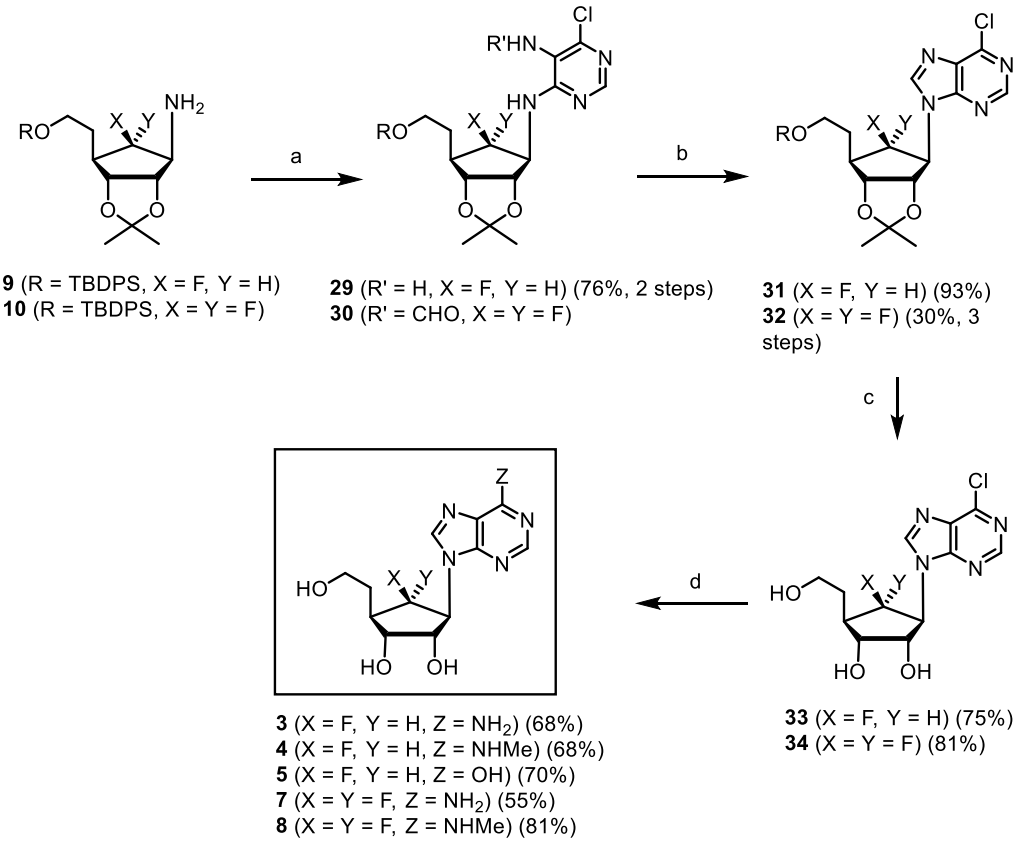
Scheme 4. Synthesis of the amine intermediate **9** and **10**.

The ketone **13** was then treated with chlorotriethylsilane and lithium bis(trimethylsilyl)amide to give silyl enol ether. The silyl enol ether was treated with selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate) which is as a conventional source of electrophilic fluorine to give the desired β-fluoro-cyclopentanone **11**. The carbanion formed at C6 attacks electrophilic fluorine, which results in the formation of the desired β-fluorinated compound **11**, because of the steric

hindrance by the 2,3-isopropylidene ring. The di-fluorinated compound **12** was also synthesized from **11** by using same procedure in 50% yield.

With the desired fluorinated sugar **11** in hand, our purpose was to synthesize fluorinated aristeromycin. . First of all, compound **11** and **12** were reduced with sodium borohydride to give alcohol **25** and **26,** respectively, which were subjected to direct condensation reaction with the purine base under the Mitsunobu conditions. But, to our disappointment, Mitsunobu condensation failed. In addition, direct S_N2 reactions (e.g. a mesylate or a triflate displacement of **25** and **26** with the *in situ* generated anion of the purine base) were unsuccessful. In contrast, the S_N2 displacement of triflate with NaN_3 occurred assumedly because the azide anion was a linear, less bulky and more powerful nucleophile. Compound **27** and **28** were reduced to amine **9** and **10** respectively using palladium catalyst 10 wt. % on activated carbon under H_2 atmosphere.

The amine **9** was treated with 5-amino-4,6-dichloropyrimidine and triethylamine in *n*-butanol under microwave irradiation to give **29**. However, difluorinated amine **10** was decomposed in microwave. So, 4,6-dichloro-5-foramidopyrimidine was added to the difluorinated amine **10** at a reflux condition. As 4,6-dichloro-5-foramidopyrimidine was more stronger electrophile than 5-amino-4,6-dichloropyrimidine, compound **30** could be formed. Further, the cyclization of compound **29** and **30** using diethoxymethyl acetate gave the desired purine nucleoside **31** and **32** (Scheme 5). Interestingly, the ^1H NMR spectrum of purine nucleoside **31** and **32** displayed doublet signals for the C8 position's proton of purine base. This could arise from the long range coupling between the proton and the fluorine atom at C6′ position, therefore, confirming the desired orientation of the fluorine atom as well as the nucleobase.



Reagent and Conditions: (a) 5-amino-4,6-dichloropyrimidine (for **29**) or 4,6-dichloro-5-foramidopyrimidine (for **30**), *N*,*N*-diisopropylethylamine, *n*-BuOH, MW, 170 °C, 10 h; (b) $CH_3C(O)OCH(OEt)_2$, 120 °C, 14 h; (c) 50% aq. TFA (for **33**), 70% aq. TFA (for **34**), MeOH, 0 °C to rt, 2 h; (d) NH_3/*t*-BuOH, 90 °C, 3 h (for **3**) or NH_3/MeOH, 70 °C, overnight (for **7**) or 40% aq. $MeNH_2$, 80 °C, 5 h (for **4** and **8**) or 1 N HCl, 1,4-dioxane, reflux, overnight (for **5**).

Scheme 5. Synthesis of the fluorinated homoaristeromycin analogues.

Removal of the acetonide and TBDPS protecting groups of the nucleoside **31** and **32** by 50% aqueous trifluoroacetic acid gave the nucleoside **33** and **34**, respectively. For synthesis of the adenine nucleoside, saturated *tert*-butanolic ammonia (saturated methanolic ammonia solution for difluorinated compound **7**) was added to the 6-chloropurine nucleoside **33** and **34** in steel bomb. Moreover, 40 wt. % aqueous methylamine was used

in steel bomb for synthesis of the *N*-methyl adenine nucleoside **4** and **8**. The hypoxanthine **5** was also synthesized in acidic condition through hydrolysis. The structure of **3** was confirmed by a single-crystal X-ray analysis (Figure 5).

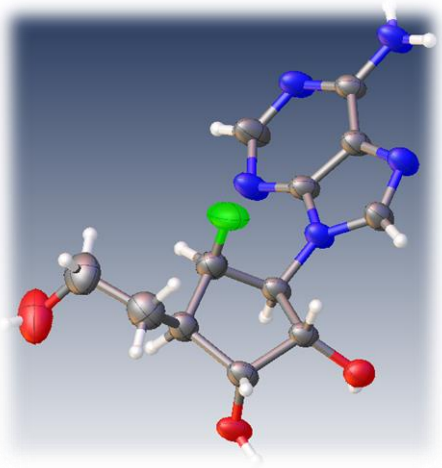
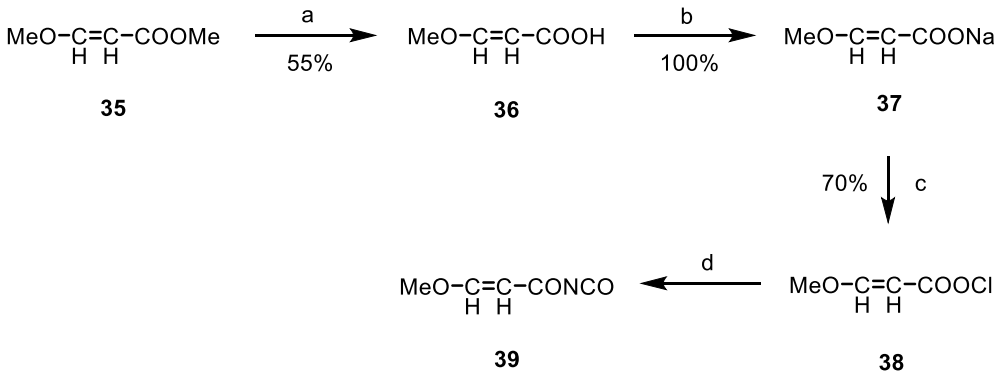


Figure 5. The crystal structure of **3** confirmed by X-ray crystallographic data analysis.

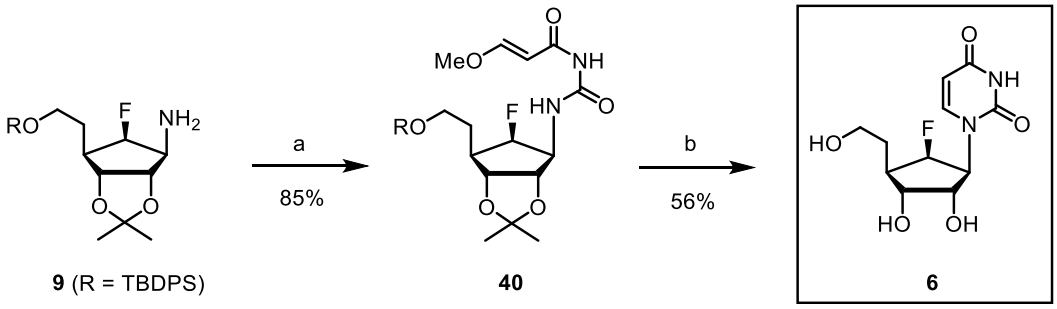
Thus, our synthetic strategy led to an efficient synthesis of the fluorinated homoaristerommycin analogue in purine base. This gives new insights for development of novel fluorinated aristeromycin analogues.



Reagent and Conditions: (a) 2 M NaOH, 2 M HCl, rt, 2 h; (b) 2 M NaOH, rt, 5 min; (c) $SOCl_2$, Et_2O, reflux, 4 h; (d) AgNCO, C_6H_6, reflux, 30 min.

In an attempt towards the synthesis of the pyrimidine analogue, we directly tried to construct the uracil base from the amine **9**. We used commercially available methyl 3-methoxy-2-propenoate **35** for the preparation of 3-methxoy-2-propenoyl isocyanate **39**, which is suitable for formation of the uracil base.

Scheme 5. Synthesis of 3-methoxy-2-propenoyl isocyanate **39**.[14]



Reagent and Conditions: (a) MeOCHCHCONCO, benzene, 4 Å molecular sieves, DMF, –20 °C to rt, 15 h; (b) 2 M H_2SO_4, reflux, 30 min.

Scheme 6. Synthesis of the uracil derivative **6** of the fluorinated homoaristeromycin.

Synthesis of isocyanate **39** began with hydrolysis of methyl 3-methoxy-2-propenoate **35** at room temperature in basic condition. The resulting acid **36**, as its sodium salt **37**, was treated with thionyl chloride in dry ether, to afford the corresponding acid chloride **38**, which was purified by vacuum distillation. Reaction of **38** with silver cyanate in benzene afforded the desired isocyanate **39**, which was not isolated due to its known instability. Compound **9** in DMF was then treated with 3-methoxy-propenoyl isocyanate **39** along with molecular sieves at −20 °C and then gradually warmed to room temperature to obtain compound **40**. This was immediately subjected to cyclization, followed by deprotection reaction using 2 M H_2SO_4 to give the uracil compound **6**.

compound	**SAH Hydrolase IC_{50} (μM)**	**MERS-CoV**		**Chikungunya virus**		**Zika virus**	
		EC_{50} (μM)	**CC_{50} (μM)**	**EC_{50} (μM)**	**CC_{50} (μM)**	**EC_{50} (μM)**	**CC_{50} (μM)**
3	**0.36**	>50	12.5	**0.12**	>250	>50	ND
7	1.72	ND	NA	NA	>25	NA	ND

***MERS-CoV: Middle East respiratory syndrome-related coronavirus**

Table 1. Results for the antiviral activity observed for compounds **3** and **7**.

The synthesized compound **3** and **7** were assayed for their antiviral activities against MERS-CoV, Chikungunya and Zika virus. Biological evaluation of the other compounds will be performed in the near future. As a result, *β*-fluoro-homoaristeromycin **3** showed inhibition of SAH hydrolase and potent antiviral activity against Chikungunya virus without cytotoxicity. These results demonstrate that *β*-fluoro-homoaristeromycin **3** may be a potential candidate as an anti-Chikungunya agent.

III. Conclusion

Based on the structure of (–)-aristeromycin, fluorinated homo-aristeromycin analogues were designed and synthesized from D-ribose via Michael reaction and stereoselective electrophilic fluorination as a key step. The β-Fluoro-homoaristeromycin **3** showed potent anti-Chikungunya (EC_{50} = 0.12 μM) without cytotoxicity up to 250 μM, showing high selectivity index (CC_{50}/EC_{50} > 2083). Compound **3** also exhibited potent inhibitory activity (IC_{50} = 1.72 μM) against SAH hydrolase. One carbon homologation of (–)-aristeromycin might prevent 5′-phosphorylation, which resulted in a low cytotoxicity. Antiviral activity seems to be correlated with SAH hydrolase inhibitory activity.

It is believed that this study will contribute greatly to the development of potent antiviral agents.

IV. Experimental Section

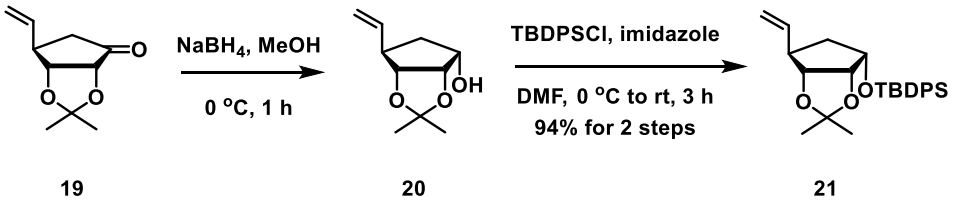
1. General Procedure

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Jeol JNMLA300 (300/75 MHz), Bruker AV 400 (400/100 MHz), Bruker AMX 500 (500/125 MHz), Jeol JNM-ECA600 (600/150 MHz), or Bruker AVANCE III 800 (800/200 MHz) spectrometer. Chemical shifts are reported in ppm units with Me_4Si or NMR solvent as the internal standard. All reactions were routinely carried out under an inert atmosphere of dry nitrogen. Reactions were checked by thin layer chromatography (Kieselgel 60 F254, Merck). Spots were detected by viewing under a UV light, and by colorizing with charring after dipping in a *p*-anisaldehyde solution or phosphomolybdic acid solution. In aqueous work-up, all

organic solutions were dried over anhydrous magnesium sulfate and filtered prior to rotary evaporation at water pump pressure. The crude compounds were purified by column chromatography on a silica gel (Kieselgel 60, 70-230 mesh, Merck). Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. All solvents were purified and dried by standard techniques just before use. THF and Et_2O were freshly distilled from sodium and benzophenone. Methylene chloride, toluene, and benzene were purified by refluxing with CaH_2. Hexanes and ethyl acetate were purified by simple distillation.

2. Experimental Procedures

Preparation of 21

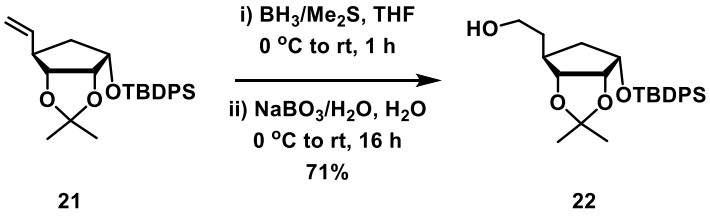


19 20 21

***tert*-Butyl(((3a*R*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-vinyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)oxy)diphenylsilane (21).** To a stirred solution of **19** (8.2 g, 45.0 mmol) in methanol (500 mL) was added sodium borohydride (2.2 g, 58.5 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The mixture was quenched with water (20 mL) and concentrated *in vacuo*. The residue was diluted with brine and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude alcohol, which was used for the next reaction without further purification. To a stirred solution of crude alcohol **20** and imidazole (15.3 g, 224.5 mmol) in *N*,*N*-dimethylformamide (240 mL) was added TBDPSCl (18.7 mL, 71.85 mmol) at 0 °C, under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h, quenched with water (150 mL) and extracted with diethyl ether (2 × 300 mL). The

combined organic layers were washed with water (5 × 200 mL), dried using anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes:ethyl acetate = 99:1) to obtain **21** as colorless syrup (18.7 g, 99%): $[\alpha]_D^{25}$ –59.2 (*c* 0.125, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 4H), 7.40 (m, 6H), 5.55 (ddd, *J* = 6.0, 10.4, 17.2 Hz, 1H), 4.85 (dt, *J* = 1.2, 9.2 Hz, 1H), 4.76 (dt, *J* = 2.0, 17.6 Hz, 1H), 4.26 (m, 1H), 4.03 (m, 1H) 2.60 (m, 2H), 2.06 (m, 1H), 1.61 (m, 1H), 1.57 (s, 3H), 1.32 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz $CDCl_3$) δ 138.6, 136.0, 129.7, 127.7, 114.7, 84.3, 79.8, 73.4, 44.1, 34.7, 27.1, 26.5, 24.8, 19.4; HRMS (FAB) found 445.2165 [calcd for $C_{26}H_{34}NaO_3Si^+$ $(M + Na)^+$ 445.2169].

Preparation of 22

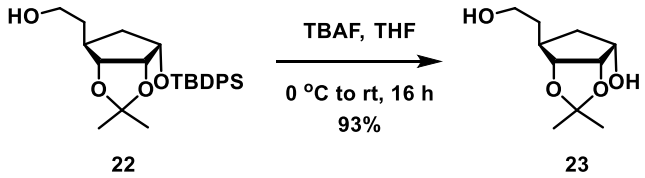


21 22

2-((3a*R*,4*S*,6*S*,6a*R*)-6-((tert-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)ethan-1-ol (22). To a stirred solution of **21** (1.72 g, 4.07 mmol) in anhydrous tetrahydrofuran (35 mL) was carefully added borane-dimethyl sulfide complex (1.0 M solution in tetrahydrofuran, 8.95 mL, 8.95 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and cooled to 0 °C, before sodium perborate (1.34 g, 13.43 mmol) and water (40 mL) were carefully added. The mixture was stirred at room temperature for 16 h, diluted with brine (10 mL) extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 4:1) to obtain **22** as colorless syrup (1.22 g, 71%): $[\alpha]_D^{25}$ –40.1 (*c* 0.187, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 4H), 7.40 (m, 6H), 4.26 (m,

2H), 4.18 (m, 1H), 4.05 (m, 1H), 3.53 (m, 1H), 1.99 (m, 1H) 1.55 (s, 3H), 1.35 (s, 3H), 1.35 (m, 1 H), 1.32 (s, 3H), 1.26 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz $CDCl_3$) δ 136.0, 134.4, 129.7, 127.7, 117.7, 84.8, 80.1, 78.2, 61.5, 38.3, 36.6, 35.5, 27.1, 26.5, 24.8, 19.4; HRMS (FAB) found 463.2281 [calcd for $C_{26}H_{36}NaO_4Si^+$ $(M + H)^+$ 463.2275].

Preparation of 23



22 23

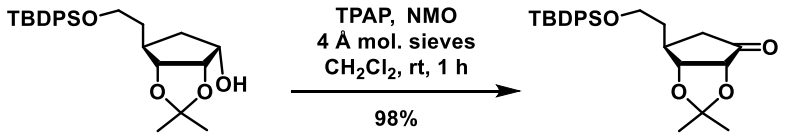
(3a*S*,4*S*,6*S*,6a*R*)-6-(2-Hydroxyethyl)-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-ol (23). To a stirred solution of **22** (7.5 g, 17.0 mmol) in anhydrous tetrahydrofuran (200 mL) was added tetra-*n*-butylammonium fluoride (1.0 M solution in tetrahydrofuran, 51.0 mL, 51.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (methylene chloride:methanol = 9:1) to obtain **23** as colorless syrup (3.3 g, 93%): $[\alpha]_D^{25}$ –8.26 (*c* 0.121, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (t, *J* = 5.9 Hz, 1H), 4.36 (dd, *J* = 5.9, 2.4 Hz, 1H), 4.07 (m, 1H), 3.69 (t, *J* = 6.1 Hz, 2H), 2.56 (br, 1H), 2.19 (m, 2H), 2.05 (br, 1H), 1.94 (dt, *J* = 13.2, 6.5 Hz, 1H), 1.62 (dt, *J* = 13.2, 6.1 Hz , 1H), 1.55 (m, 2H), 1.51 (m, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.4, 85.1, 79.5, 70.6, 61.4, 38.8, 37.5, 35.2, 26.1, 24.1; HRMS (FAB) found 203.1274 [calcd for $C_{10}H_{19}O_4^+$ $(M + H)^+$ 203.1278].

Preparation of 24

23 24

(3a*S*,4*S*,6*S*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-ol (24). To a stirred solution of **23** (3.3 g, 16.3 mmol), triethylamine (6.8 mL, 48.9 mmol) and 4-*N*,*N*-dimethylaminopyridine (0.2 g, 1.6 mmol) in methylene chloride (40 mL) was added TBDPSCl (4.9 g, 17.9 mmol) at 0 °C, under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature, quenched with water (5 mL) and extracted with methylene chloride (2 × 40 mL). The organic portion was dried using anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes:ethyl acetate = 4:1) to obtain **24** as colorless oil (5.7 g, 80%): $[\alpha]_D^{25}$ –20.4 (*c* 0.093, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.42 (m, 6H), 4.43 (t, *J* = 5.6 Hz, 1H), 4.34 (dd, *J* = 1.2, 6 Hz, 1H), 4.02 (m, 1H), 3.72 (m, 2H), 2.47 (d, *J* = 7.6 Hz, 1H), 2.19 (m, 1H), 1.87 (m, 1 H), 1.68 (m, 1 H), 1.56 (m, 1 H), 1.51 (s, 3H), 1.46 (m, 1H), 1.34 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 135.7, 133.8, 129.7, 111.5, 85.1, 79.1, 71.3, 62.5; HRMS (FAB) found 441.2458 [calcd for $C_{26}H_{36}NaO_4Si^+$ $(M + H)^+$ 441.2456].

Preparation of 13

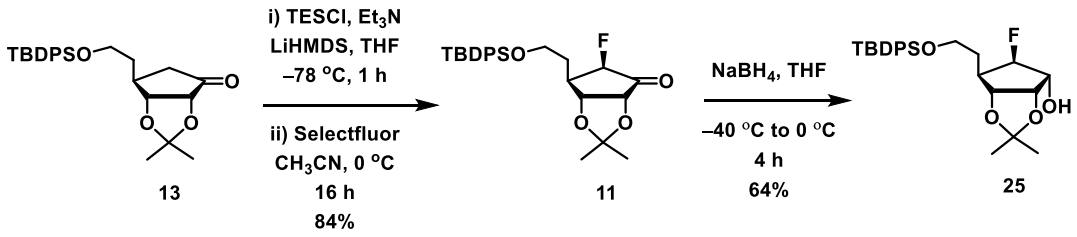


24 13

(3a*R*,6*S*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-one (13). To a stirred solution of **24** (1.04 g, 2.36 mmol) in

methylene chloride (50 mL) were added 4 Å molecular sieves (1.04 g), 4-*N*-methylmorpholine-*N*-oxide (0.55 g, 4.72 mmol) and tetra-*n*-propylammonium perruthenate (TPAP) (33 mg, 0.094 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h and filtered through a pad of Celite and silica. The filtrates was concentrated to give a residue, which was purified by silica gel column chromatography (hexanes:ethyl acetate = 2.3:1) to obtain **13** as a colorless syrup (1.13 g, 99%): $[\alpha]_D^{25}$ – 84.1 (*c* 0.12, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.41 (m, 6H), 4.57 (d, *J* = 5.6 Hz, 1H), 4.17 (m, 1H), 3.72 (m, 3H), 2.73 (dd, *J* = 8.8, 18.4 Hz, 1H), 2.61 (m, 1H), 2.03 (dt, *J* = 1.6, 17.6 Hz, 1H), 1.68 (m, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 135.7, 133.5, 130.0, 127.9, 112.3, 82.2, 78.3, 61.7, 40.1, 36.2, 34.0, 27.0, 25.1, 19.3; HRMS (FAB) found 456.2572 [calcd for $C_{26}H_{38}NO_4Si^+$ (M + NH_4)$^+$ 456.2565].

Preparation of 25



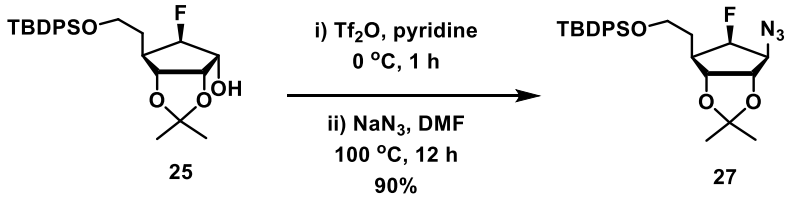
(3a*S*,4*R*,5*R*,6*R*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-5-fluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-ol (25). To a stirred solution of **13** (6.4 g, 14.5 mmol) in anhydrous tetrahydrofuran (105 mL) at –78 °C, under nitrogen atmosphere were added chlorotrietylsilane (9.73 mL, 58.0 mmol) and lithium *bis* (trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 29.0 mL, 29.0 mmol). The reaction mixture was stirred at –78 °C for 1 h, warmed to 0 °C and quenched using saturated aqueous NH_4Cl (30 mL). The solution was extracted with ethyl acetate (2 × 100 mL). The

combined organic layers were dried using anhydrous $MgSO_4$ and concentrated *in vacuo* to get the crude silyl enol ether, which was used immediately for the next step without further purification.

To a stirred solution of the crude silyl enol ether in anhydrous acetonitrile (120 mL) was added Selectfluor® (7.7 g, 21.8 mmol) at 0 °C. The reaction mixture was stirred for 16 h at 0 °C, diluted with brine (50 mL) and extracted with ethyl acetate (2 × 100) . The organic layers were dried using anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 5.6:1) to obtain an inseparable mixture of the mono fluoroketone **11** and the mono fluoro geminal diol (3.7 g, 84%).

To a stirred solution of **11** (4.06 g, 8.89 mmol) in tetrahydrofuran (120 mL) was slowly added sodium borohydride (0.5 mg, 13.34 mmol) at –40 °C. The reaction mixture was stirred at –40 °C for 1 h and then warmed to 0 °C. The mixture was stirred at 0 °C for 3 h, diluted with water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes:ethyl acetate = 11.5:1) to obtain **25** as colorless oil (2.62 g, 64%); $[\alpha]_D^{25}$ –43.5 (*c* 0.14, CH_3OH): ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.40 (m, 6H), 4.9 (ddd, *J* = 3.6, 4.4, 50.8 Hz, 1H), 4.64 (m, 1H), 4.54 (m, 1H), 4.08 (m, 1H), 3.75 (m, 1H), 2.73 (dd, *J* = 2.8, 4.4 Hz, 1H), 2.48 (m, 1H), 1.89 (m, 1H), 1.66 (m, 1H), 1.51 (s, 3H), 1.34 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 133.9, 129.8, 113.8, 101.6, 99.8, 84.0, 78.2, 72.3 (*J* = 27.5 Hz), 62.5, 43.5 (*J* = 72.0 Hz), 29.6 (*J* = 5.9 Hz), 26.5, 24.7, 19.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –204.7; HRMS (FAB) found 459.2366 [calcd for $C_{26}H_{36}FO_4Si^+$ $(M + H)^+$ 459.2361].

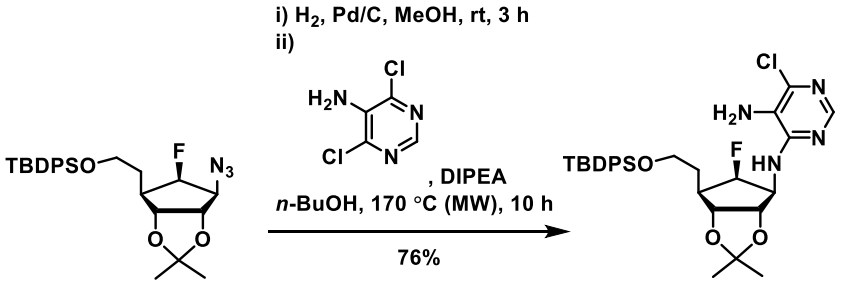
Preparation of 27



(2-((3a*R*,4*R*,5*R*,6*S*,6a*S*)-6-Azido-5-fluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)ethoxy)(tert-butyl)diphenylsilane (27). To a stirred solution of **25** (2.35 g, 5.12 mmol) in anhydrous pyridine (50 mL) was added triflic anhydride (1.72 mL, 10.24 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, quenched with water (3 mL) and concentrated *in vacuo*. The residue was diluted with ethyl acetate (100 mL) and washed with 15% aqueous $CuSO_4$ solution (3 × 30 mL). The organic portion was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to get the crude triflate, which was used immediately for the next step without further purification.

To a stirred solution of the crude triflate in anhydrous *N*,*N*-dimethyl formamide (50 mL) was added sodium azide (3.08 g, 51.2 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 12 h, cooled to room temperature and diluted with water (10 mL). The solution was extracted with diethyl ether (100 mL). The organic portion was washed with water (5 × 50 mL), dried using anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 32.3:1) to obtain **27** as colorless oil (0.36 g, 90%): $[\alpha]_D^{25}$ –98.7 (*c* 0.155, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.41 (m, 6H), 4.92 (dt, *J* = 3.2, 52.8 Hz, 1 H), 4.68 (m, 1H), 4.45 (m, 1H), 3.79 (m, 2H), 3.67 (m, 1H), 2.34 (m, 1H), 1.87 (m, 1H), 1.52 (s, 3H), 1.32 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 133.8, 129.9, 127.8, 114.2, 99.4, 97.6, 83.6, 82.3, 68.3 (*J* = 15.7 Hz), 61.9, 45.5 (*J* = 17.7 Hz), 30.3 (*J* = 4.6 Hz), 27.4, 24.9, 19.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –205.5; HRMS (FAB) found 506.2254 [calcd for $C_{26}H_{34}FN_3NaO_3Si^+$ $(M + Na)^+$ 506.2246].

Preparation of 29

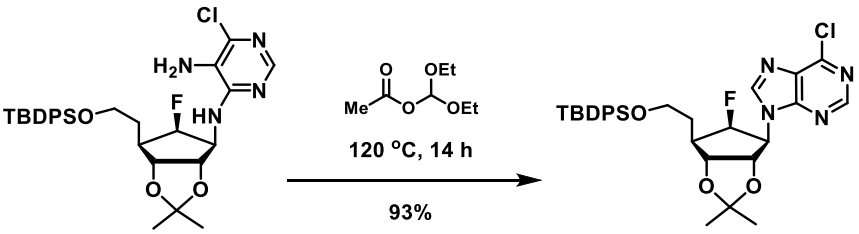


27 29

***N*^{4}-((3a*S*,4*S*,5*R*,6*R*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-5-fluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)-6-chloropyrimidine-4,5-diamine (29).** To a stirred solution of **27** (0.991 g, 2.04 mmol) in methanol (50 mL) was added 10% palladium/carbon (wetted with ca. 55% water) (250 mg) at room temperature. The reaction mixture was stirred under H_2 for 3 h. After completion of reaction (TLC), the suspension was filtered through a pad of Celite and concentrated to obtain the amine as colorless syrup, which was used for the next step without further purification.

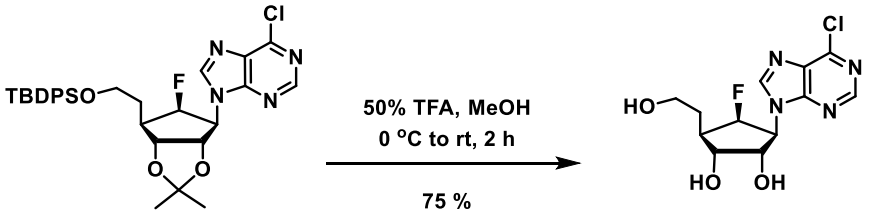
To a solution of the crude amine (0.933 g, 2.04 mmol) in *n*-butanol (20 mL) were added 5-amino-4,6-dichloropyrimidine and *N*,*N*-diisopropylethylamine at room temperature. The reaction mixture was subjected to microwave irradiation at 170 °C for 10 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate (30 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes:ethyl acetate = 4.6:1) to obtain **27** as colorless oil (0.91 g, 76%): $[\alpha]_D^{25}$ –19.7 (*c* 0.167, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.60–7.64 (m, 4H), 7.44–7.34 (m, 6H), 5.33 (d, *J* = 7.9 Hz), 5.05 (dt, *J* = 3.0, 53.3 Hz, 1H), 4.75–4.64 (m, 1H), 4.61 (merged dd, $J_1 = J_2$ = 6.7 Hz, 1H), 4.44 (merged dd, $J_1 = J_2$ = 6.7 Hz, 1H), 3.82–3.71 (m, 2H), 3.60–3.45 (brs, 2 H), 2.51–2.37 (m, 1H), 1.94–1.80 (m, 2H), 1.54 (s, 3H), 1.30 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.3, 149.3, 143.2, 135.5, 133.6, 129.6, 127.6, 122.3, 114.1, 98.3 (*J* = 211.8 Hz), 84.1, 83.4, 61.8, 60.3 (*J* = 19.4 Hz), 45.6 (*J* = 21.8 Hz), 30.4 (*J* = 5.6), 27.3, 26.8, 24.9, 19.1 ^{19}F NMR (376 MHz, $CDCl_3$) δ –208.0; HRMS (FAB) found 585.2468 [calcd for $C_{30}H_{39}ClFN_4O_3Si^+$ $(M + H)^+$ 585.2458].

Preparation of 31



9-((3a*S*,4*S*,5*R*,6*R*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-5-fluoro-2,2-Dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)-6-chloro-9H-purine (31). To a stirred solution of **29** (0.91 g, 1.56 mmol) in diethoxymethyl acetate (15 mL) was heated at 120 °C for 14 h. The reaction was cooled and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (hexanes:ethyl acetate = 9:1) to obtain **31** as a white foam (0.87 g, 93%): $[\alpha]_D^{25}$ –12.3 (*c* 0.162, CH_3OH); UV (CH_3OH) λ_{max} 263 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.32 (d, *J* = 2.4 Hz, 1H), 7.68 (m, 4H), 7.4 (m, 6H), 5.18 (m, 1H), 5.08 (m, 2H), 4.62 (m, 1H), 3.81 (m, 2H), 2.64 (m, 1H), 1.95 (m, 2H), 1.59 (s, 3H), 1.34 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 144.2, 135.7, 133.7, 129.9, 127.9, 115.3, 99.2, 97.4, 83.4, 83.0, 63.3, 61.7, 46.0, 30.5, 27.6, 27.0, 25.1, 19.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –200.72; HRMS (FAB) found 595.2290 [calcd for $C_{31}H_{37}ClFN_4O_3Si^+$ $(M + H)^+$ 595.2302].

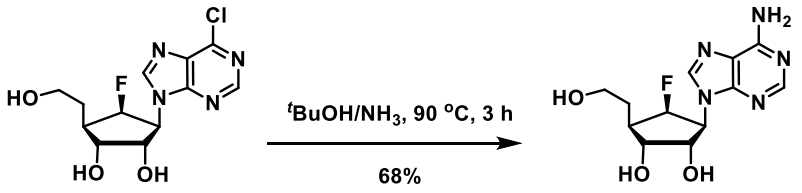
Preparation of 33



31 33

(1*R*,2*S*,3*S*,4*R*,5*R*)-3-(6-Chloro-9*H*-purin-9-yl)-4-fluoro-5-(2-hydroxyethyl)cyclopentane-1,2-diol (33). To a stirred solution of **31** (0.57 g, 0.966 mmol) in methanol (3 mL) was added 50% aqueous trifluoroacetic acid (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (methylene chloride:methanol = 9:1) to obtain **33** (0.23 g, 75%), which was crystallized from diethyl ether/methanol: white solid; mp 147–149 °C; $[\alpha]_D^{25}$ –32.7 (*c* 0.107, CH_3OH); UV (CH_3OH) λ_{max} 263.5 nm; ^1H NMR (400 MHz, CD_3OD) δ 8.75 (s, 1H), 8.71 (d, *J* = 2.4 Hz, 1H), 5.18 (dt, *J* = 4.0, 51.6 Hz, 1H), 5.15, (m, 1H), 4.80 (m, 1H), 4.06 (t, 5.4 Hz, 1H), 3.72 (m, 2H), 2.41 (m, 1H), 1.9 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 154.0, 153.2, 151.4, 147.4 (*J* = 3.62 Hz), 94.3, 92.5, 74.5, 73.7, 64.3 (*J* = 17.3 Hz), 31.8 (*J* = 7.1 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –204.34; HRMS (FAB) found 317.0810 [calcd for $C_{12}H_{12}ClFN_4O_3^+$ $(M + H)^+$ 317.0811].

Preparation of 3

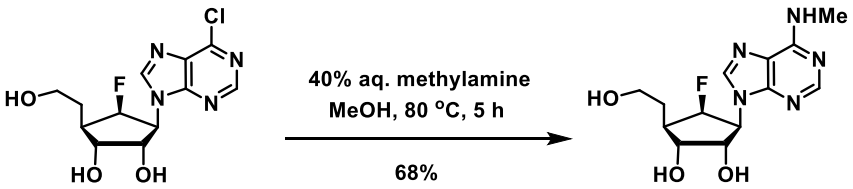


33 3

(1*R*,2*S*,3*S*,4*R*,5*R*)-3-(6-Amino-9*H*-purin-9-yl)-4-fluoro-5-(2-hydroxyethyl)cyclopentane-1,2-diol (3). A steel pressure vessel containing a solution of

33 (70 mg, 0.22 mmol) in saturated *tert*-butanolic ammonia was heated at 90 °C for 3 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (methylene chloride:methanol = 5:1) to obtain **3** (44 mg, 68%), which was crystallized from diethyl ether/methanol: white solid; mp 168–170 °C; $[\alpha]_D^{25}$ –49.3 (*c* 0.146, CH_3OH); UV (CH_3OH) λ_{max} 259 nm, ^1H NMR (400 MHz, CD_3OD) δ 8.26 (d, *J* = 2.0 Hz, 1H), 8.20 (s, 1H), 5.11 (dt, *J* = 3.6, 55.2 Hz, 1H), 4.99 (ddd, *J* = 3.2, 9.6, 26.4 Hz, 1H), 4.75 (m, 1H), 4.04 (m, 1H), 3.71 (m, 2H), 2.38 (m, 1H), 1.89 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.4, 153.9, 151.5, 141.7 (*J* = 4.4 Hz), 94.2, 92.6, 74.5, 73.7, 63.7 (*J* = 17.1 Hz), 61.1, 47.8, (*J* = 17.9 Hz), 31.8 (*J* = 6.6 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –204.9; HRMS (FAB) found 298.1310 [calcd for $C_{12}H_{17}FN_5O_3^+$ $(M + H)^+$ 298.1310].

Preparation of 4

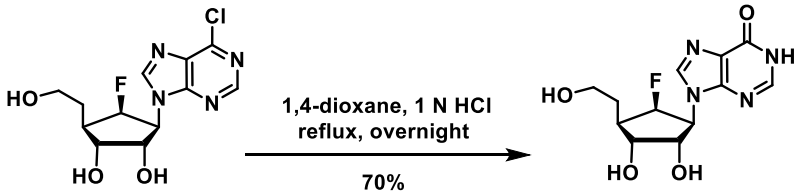


33 4

(1*S*,2*R*,3*R*,4*R*,5*S*)-4-Fluoro-3-(2-hydroxyethyl)-5-(6-(methylamino)-9*H*-purin-9-yl)cyclopentane-1,2-diol (4). A steel pressure vessel containing a solution of **33** (55 mg, 0.17 mmol) in methanol was added methylamine solution 40 wt.% in H_2O. The reaction mixture was heated at 80 °C for 5 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (methylene chloride:methanol = 5:1) to obtain **4** (37 mg, 68%), which was crystallized from diethyl ether/methanol: white solid; mp 171–173 °C; $[\alpha]_D^{20}$ –1.06 (*c* 0.160, CH_3OH); UV (CH_3OH) λ_{max} 265 nm; ^1H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.2 (d, *J* = 1.4 Hz,

1H), 5.09 (dt, *J* = 3.6, 54.8 Hz, 1H), 4.96 (ddd, *J* = 3.0, 9.4, 26.7 Hz, 1H), 4.74 (t, *J* = 7.4 Hz, 1H), 4.02 (t, *J* = 6.0 Hz, 1H), 3.74–3.67 (m, 2H), 3.20–3.00 (brs, 3H), 2.42–2.31 (m, 1H), 1.94–1.84 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 157.5, 154.6, 151.1, 141.8 (*J* = 3.6 Hz), 121.1, 94.2 (*J* = 180.5 Hz), 75.3, 74.4, 64.4 (*J* = 17.0 Hz), 61.8, 48.5 (*J* = 18.5 Hz), 32.6 (*J* = 6.6 Hz), 28.6; ^{19}F NMR (376 MHz, CD_3OD) δ –206.4; HRMS (FAB) found 312.1460 [calcd for $C_{13}H_{19}FN_5O_3^+$ $(M + H)^+$ 312.1466].

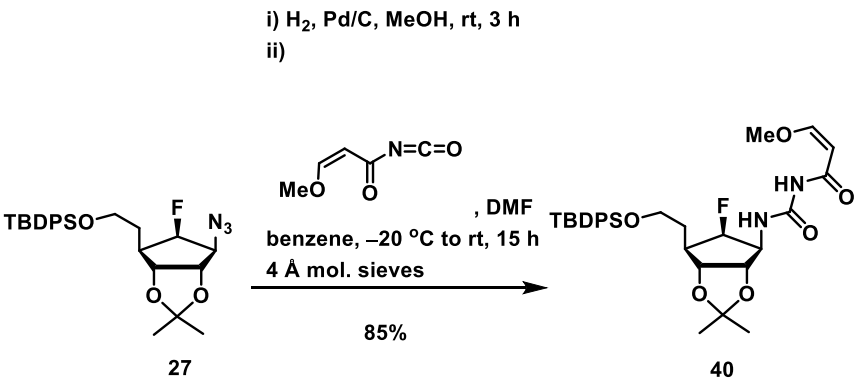
Preparation of 5



33 5

9-((1*S*,2*R*,3*R*,4*R*,5*S*)-2-Fluoro-4,5-dihydroxy-3-(2-hydroxyethyl)cyclopentyl)-1,9-dihydro-6*H*-purin-6-one (5). To a stirred solution of **33** (50 mg, 0.158 mmol) in 1,4-dioxane (3 mL) was added 1 N HCl (3 mL) at room temperature. The reaction mixture was heated at reflux overnight, cooled to room temperature and concentrated *in vacuo*. The residue was purified by C-18 reverse-phase silica gel column chromatography (H_2O) to give **5** (33 mg, 70%), which was crystallized from diethyl ether/methanol: white solid; mp 184–186 °C; $[\alpha]_D^{20}$ –33.25 (*c* 0.160, H_2O); UV (H_2O) λ_{max} 250 nm; ^{1}H NMR (800 MHz, D_2O) δ 8.20 (s, 1H), 8.08 (s, 1H), 5.07 (dt, *J* = 3.7, 54.2 Hz, 1H), 4.91 (ddd, *J* = 3.2, 9.8, 30.2 Hz, 1H), 4.74-4.72 (m, 1H), 4.05 (t, *J* = 5.9 Hz, 1H), 3.65 (t, *J* = 6.6 Hz, 2H), 2.33-2.25 (m, 1H), 1.87-1.77 (m, 2H); ^{13}C NMR (150 MHz, D_2O) δ 158.4, 149.4, 145.7, 141.0, 123.0, 91.9 (*J* = 179.9 Hz), 72.5, 72.1, 61.8 (*J* = 16.9 Hz), 59.6, 45.5 (*J* = 18.5 Hz), 29.4 (*J* = 6.9 Hz)); ^{19}F NMR (376 MHz, CD_3OD) δ -204.9; HRMS (FAB) found 299.1150 [calcd for $C_{12}H_{16}FN_4O_5^+$ $(M + H)^+$ 299.1150].

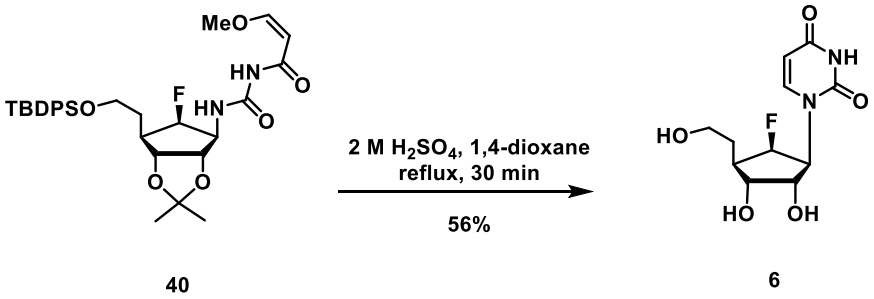
Preparation of 40



(Z)-*N*-(((3a*S*,4*S*,5*R*,6*R*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-5-fluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)carbamoyl)-3-methoxyacrylamide (35). To a stirred solution of **27** (0.2 g, 0.41 mmol) in methanol (15 mL) was added Pd/C (10%, 50 mg) at room temperature. The reaction mixture was stirred under H_2 for 3 h. The suspension was filtered through Celite and concentrated *in vacuo* to obtain the crude amine as colorless syrup, which was used for the next step without further purification. To a stirred solution of the crude amine in *N*,*N*-dimethylformamide (4 mL) was added solution of isocyanate compound **39** (0.1 g, 0.82 mmol) in anhydrous benzene (3 mL) at –20 °C over 4 Å molecular sieves under N_2 atmosphere. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was filtered and concentrated *in vacuo* (co-evaporation with toluene and ethanol), maintaining the temperature below 40 °C. The residue was purified by silica gel chromatography (hexanes:ethyl acetate = 3:2) to obtain **40** (0.2 g, 85%): yellow syrup; $[\alpha]_D^{20}$ +11.03 (*c* 0.330, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.19 (d, *J* = 8.25, 1H), 7.69–7.66 (m, 5H), 7.43–7.36 (m, 6H), 5.40 (d, *J* = 12.3 Hz, 1H), 4.90 (dt, *J* = 3.0, 53.1 Hz, 1H), 4.57 (t, *J* = 6.3 Hz, 1H), 4.44–4.38 (m, 2H), 3.81–3.71 (m, 2H), 3.69 (s, 3H), 2.40–2.32 (m, 1H), 1.90–1.83 (m, 2H), 1.49 (s, 3H), 1.29 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 163.6, 155.3, 135.5, 133.7, 129.6, 127.6, 113.7, 98.5 (*J* = 178.4 Hz), 97.6, 84.6, 83.6, 61.6, 58.9 (*J* = 15.9 Hz), 57.7, 45.7 (*J* = 18.1 Hz), 30.3 (*J* = 4.8 Hz), 27.4, 26.8,

24.9, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –206.7; HRMS (FAB) found 585.2780 [calcd for $C_{31}H_{42}FN_2O_6Si^+$ $(M + H)^+$ 585.2791].

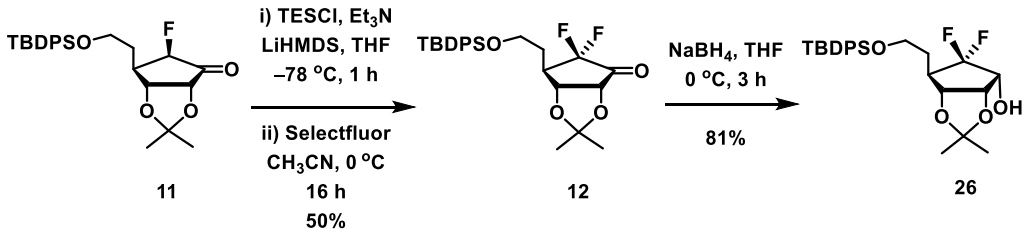
Preparation of 6



40 6

1-((1*S*,2*R*,3*R*,4*R*,5*S*)-2-Fluoro-4,5-dihydroxy-3-(2-hydroxyethyl)cyclopentyl)pyrimidine-2,4(1*H*,3*H*)-dione (6). To a stirred solution of **40** (0.16 g, 0.28 mmol) in 1,4-dioxane (3 mL) was added 2 M sulfuric acid (2 mL) at room temperature. The reaction mixture was heated at reflux for 30 min, cooled to room temperature and concentrated *in vacuo*. The residue was diluted with methanol (10 mL), neutralized by weak basic resin (DOWEX® 66 ion-exchange resin), filtered and concentrated *in vacuo* to get the crude uracil, which was purified by silica gel chromatography (methylene chloride:methanol = 9:1) to give **6** (43 mg, 56%) and crystallized from diethyl ether/methanol: white solid; mp 87–89 °C; $[\alpha]_D^{25}$ -99.5 (*c* 0.150, CH_3OH); UV (H_2O) λ_{max} 253 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, *J* = 8.0 Hz, 1H), 5.69 (d, *J* = 8.1 Hz, 1H), 4.99 (dt, *J* = 3.6, 55.4 Hz, 1H), 4.88 (ddd, *J* =3.3, 9.8, 30.7, 1H), 4.45 (merged dd, $J_1 = J_2$ = 7.1, 1H), 3.91 (t, *J* = 5.9 Hz, 1H), 3.71–3.64 (m, 2H), 2.29–2.20 (m, 1H), 1.88–1.75 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 167.0, 154.1, 145.6 (*J* = 3.9 Hz), 102.7, 94.3 (*J* = 180.0 Hz) 75.1, 72.4, 64.8 (*J* = 16.4 Hz), 61.8, 48.0 (J = 18.4 Hz), 32.4 (*J* = 7.4 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –209.0; HRMS (FAB) found 275.1030 [calcd for $C_{11}H_{16}FN_2O_5^+$ $(M + H)^+$ 275.1038].

Preparation of 26



(3a*S*,4*R*,6*R*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-5,5-difluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-ol (26).

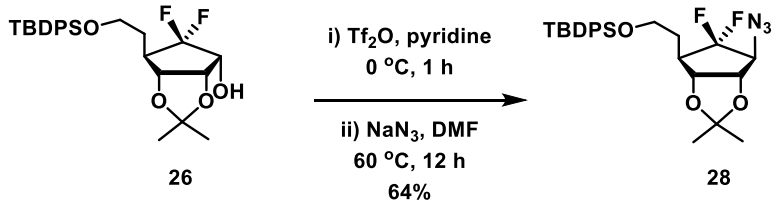
To a stirred solution of **11** (5.7 g, 10.03 mmol) in anhydrous tetrahydrofuran (100 mL) at 0 °C, under N_2 atmosphere were added triethylamine (7.0 mL, 50.15 mmol), chlorotriethylsilane (8.4 mL, 50.15 mmol) and lithium *bis* trimethylsilyl amide (1.0 M solution in tetrahydrofuran, 25.1 mL, 25.08 mmol). The reaction mixture was stirred at room temperature for 1 h, warmed to 0 °C and quenched using saturated aqueous ammonium chloride solution. The solution was extracted with ethyl acetate (2 × 100 mL). The combined organic portions were dried using $MgSO_4$ and concentrated *in vacuo* to obtain the crude silyl enol ether, which was used immediately for the next step without further purification.

To a stirred solution of the crude silyl enol ether in anhydrous acetonitrile (100 mL) was added a solution of Selectfluor® (7.11 g, 20.06 mmol) in acetonitrile (85 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, concentrated *in vacuo* and diluted with ethyl acetate (2 × 100 mL). The combined organic portions was dried using $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 2.3:1) to obtain **12** as the difluoro geminal diol (2.37 g, 50%).

To a stirred solution of **12** (2.19 g, 4.61 mmol) in tetrahydrofuran (45 mL) was added sodium borohydride (0.21 g, 5.53 mmol) at 0 °C, over a period of 15 min. The reaction mixture was stirred at 0 °C for 3 h, diluted with water (30 mL) and few drops of acetic acid and extracted with ethyl acetate (2 × 40 mL). The organic layers were washed with brine,

dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 9:1) to obtain **26** as colorless oil (1.79 g, 81%): $[\alpha]_D^{20}$ +18.8 (*c* 0.340, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.44–7.36 (m, 6H), 4.54 (m, 1H), 4.36–4.34 (m, 1H), 3.97 (ddd, *J* = 6.4, 12.5 Hz, 1H), 3.79–3.74 (m, 2H), 2.87 (d, *J* = 5.6 Hz, 1H), 2.65–2.60 (m, 1H), 1.97–1.91 (m, 1H), 1.58–1.52 (m, 4H), 1.32 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 133.5, 129.6, 128.0 (*J* = 248.8, 263.5 Hz), 127.6, 112.9, 81.1, 75.2, 71.0 (*J* = 12.4, 19.8 Hz), 61.5, 44.9 (*J* = 20.5 Hz), 28.8, 26.8, 26.0, 24.4, 19.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −112.7 (dd, *J* = 16.1, 241.9 Hz), −115.8 (dd, *J* = 24.8, 242.7 Hz); HRMS (FAB) found 494.2540 [calcd for $C_{26}H_{38}F_2NO_4Si^+$ $(M + NH_4)^+$ 494.2533].

Preparation of 28

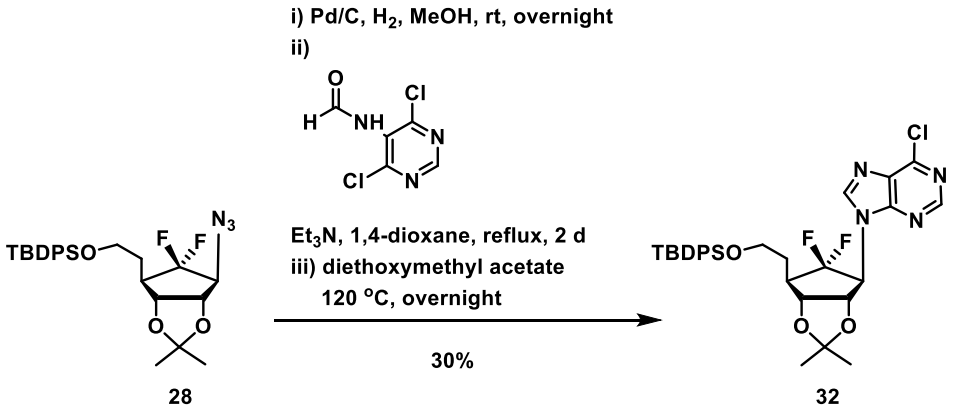


(2-((3a*R*,4*R*,6*S*,6a*S*)-6-azido-5,5-difluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)ethoxy)(tert-butyl)diphenylsilane (28). To a stirred solution of **26** (1.65 g, 3.46 mmol) in anhydrous pyridine (30 mL) was added triflic anhydride (1.16 mL 6.92 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, quenched using saturated aqueous sodium bicarbonate solution (5 mL), concentrated *in vacuo* to get the crude compound, which was diluted with ethyl acetate (40 mL), washed with 15% aqueous $CuSO_4$ solution and extracted with ethyl acetate (2 × 30 mL). The organic layers were washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The

residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 2.5:1) to obtain the triflate compound, which was used immediately for the next step.

To a stirred solution of the triflate in anhydrous *N*,*N*-dimethylformamide (30 mL) was added sodium azide (0.62 g, 10.38 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 12 h, cooled to room temperature and diluted with water (10 mL). The solution was extracted with diethyl ether (2 × 40 mL) . The organic layers were washed with water (5 × 30 mL), dried using anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 19:1) to obtain **28** as colorless oil (1.12 g, 64%): $[\alpha]^{20}_D$ +14.6 (*c* 0.335, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.67 (m, 4H), 7.44–7.36 (m, 6H), 4.40–4.38 (m, 1H), 4.30–4.27 (m, 1H), 3.94 (dt, *J* = 5.3, 17.6 Hz, 1H), 3.77 (t, *J* = 6.2 Hz, 2H), 2.66–2.59 (m, 1H), 2.02–1.96 (m, 1H), 1.75–1.68 (m, 1H), 1.52 (s, 3H), 1.28 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 133.5, 129.6, 127.6, 127.3(*J* = 270.0, 275.0 Hz), 113.5, 80.1 (*J* = 8.6 Hz), 79.5 (*J* = 7.0 Hz), 68.6 (*J* = 18.9, 22.8 Hz), 60.9, 46.5 (*J* = 20.1 Hz), 28.7 (*J* = 4.3 Hz), 29.0, 26.8, 24.7, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.5, −120.2; HRMS (FAB) found 524.2161 [calcd for $C_{26}H_{33}F_2N_3NaO_3Si^+$ $(M + Na)^+$ 524.2151].

Preparation of 32

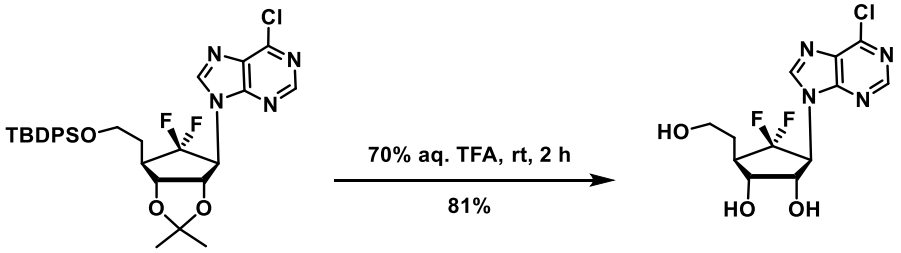


9-((3a*S*,4*S*,6*R*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-5,5-difluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)-6-chloro-9*H*-purine (32). To solution of **28** (0.93 g, 1.85 mmol) in methanol (18 mL) was added 10% palladium/carbon (wetted with ca. 55% water) (200 mg) at room temperature and the reaction mixture was exchanged with H_2 gas for three times and stirred under H_2 atmosphere at rt overnight. The suspension was filtered through Celite and concentrated to obtain the amine as colorless syrup which was used for the next step without further purification.

To a stirred solution of the crude amine in 1,4-dioxane (15 mL) were added 4,6-dichloro-5-formamidopyrimidine (0.71 g, 3.70 mmol) and triethylamine (1.9 mL, 13.60 mmol). The reaction mixture was heated at reflux for 2 d, cooled and the solvent was removed under reduced pressure and the residue was used for the next step without further purification. To the crude pyrimidine was added diethoxymethyl acetate (15 mL) and the reaction mixture was stirred at 120 °C overnight. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to obtain **32** (0.35 g, 30%) as a white foam: $[\alpha]_D^{20}$ −10.1 (*c* 0.250, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.24 (d, *J* = 1.9 Hz, 1H), 7.70−7.67 (m, 4H), 7.43−7.36 (m, 6H), 5.38−5.32 (m, 1H), 5.14 (t, *J* = 6.9 Hz, 1H), 4.52 (t, *J* = 6.4 Hz, 1H), 3.85−3.80 (m, 2H), 2.98−2.90 (m, 1H), 2.09−2.03 (m, 1H), 1.86−1.81 (m, 1H), 1.59 (s, 3H), 1.31 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 152.4, 151.6, 143.7 (J = 4.3 Hz), 135.6,

133.4, 131.4, 129.7, 127.7, 126.1(*J* = 247.5, 262.5 Hz), 114.5, 79.9 (J = 10.1 Hz), 78.8 (J = 7.2 Hz), 63.8 (J = 22.3 Hz), 60.6, 46.6 (J = 20.1 Hz), 28.6 (J = 4.3 Hz), 27.2, 26.8, 24.9, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.7, −117.1; HRMS (FAB) found 613.2213 [calcd for $C_{31}H_{36}ClF_2N_4O_3Si^+$ $(M + H)^+$ 613.2208].

Preparation of 34

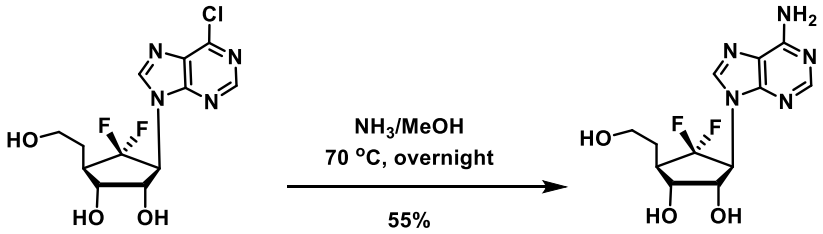


32 **34**

2-((3a*R*,4*R*,6*S*,6a*S*)-6-(6-Chloro-9*H*-purin-9-yl)-5,5-difluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)ethan-1-ol (34). To a stirred solution of **32** (0.28 g, 0.45 mmol) in 1,4-dioxane (4 mL) was added 70% aqueous trifluoroacetic acid solution (12 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (methylene chloride:methanol = 9:1) to obtain **34** (0.12 g, 81 %), which was crystallized from diethyl ether/methanol: white solid; mp 80-82 °C $[\alpha]_D^{25}$ +53.2 (*c* 0.130, CH_3OH); UV (CH_3OH) λ_{max} 264 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.77 (s, 1H), 8.76 (d, *J* = 1.9 Hz, 1H), 5.45 (ddd, $J_1 = J_2$ = 8.7 Hz, J_3 = 17.9 Hz, 1H), 4.91−4.88 (m, 1H), 4.10−4.09 (m, 1H), 3.74−3.69 (m, 2H), 2.70−2.67 (m, 1H), 2.01−1.95 (m, 1H), 1.83, 1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 154.13, 152.42, 148.46, 133.03, 126.16 (*J* = 251.0, 259.1 Hz), 74.3 (*J* = 7.1 Hz), 72.8 (*J* = 6.6 Hz), 65.9 (*J* = 23.0 Hz), 61.2, 31.3 (*J* = 6.8 Hz), 61.2, 31.3 (*J* = 6.8 Hz) (1 carbon hidden by methanol peak); ^{19}F NMR (376 MHz, CD_3OD) δ −

103.3, −115.9; HRMS (FAB) found 335.0713 [calcd for $C_{12}H_{14}ClF_2N_4O_3^+$ $(M + H)^+$ 335.0717].

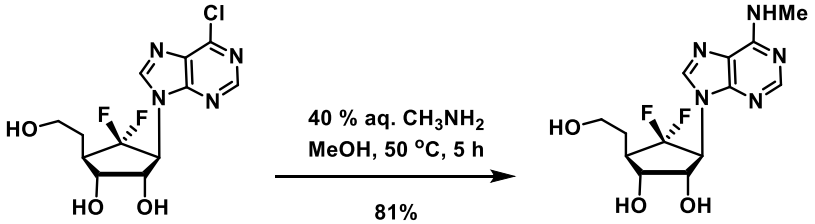
Preparation of 7



34 7

2-((3a*R*,4*R*,6*S*,6a*S*)-6-(6-Amino-9*H*-purin-9-yl)-5,5-difluoro-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)ethan-1-ol (7). A steel pressure vessel containing a solution of **34** (33 mg g, 0.099 mmol) in saturated methanolic ammonia (20 mL) was heated at 70 °C overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (methylene chloride:methanol = 9:1) to obtain **7** (0.012 g, 55% based on recovered starting material), which was crystallized from diethyl ether/methanol: white solid; mp 109−111 °C; $[\alpha]_D^{20}$ +131.8 (*c* 0.040, CH_3OH); UV (CH_3OH) λ_{max} 261 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.27 (d, *J* = 1.8 Hz, 1H), 8.20 (s, 1H), 5.29 (ddd, $J_1 = J_2$ = 8.4 Hz, J_3 = 17.8 Hz, 1H), 4.77 (dd, *J* =6.6, 8.8 Hz, 1H), 4.07 (t, *J* = 4.8 Hz, 1H), 3.74–3.69 (m, 2H), 2.69–2.62 (m, 1H), 2.00−1.94 (m, 1H), 1.83–1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 154.8, 152.6, 142.7, 126.1 (*J* = 251.3, 258.5 Hz), 120.6, 74.0 (*J* = 7.9 Hz), 73.0 (*J* = 6.5 Hz), 65.2 (*J* = 21.6 Hz), 61.3, 50.7, 31.3 (*J* = 6.5 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −103.3, −115.9; HRMS (FAB) found 316.1220 [calcd for $C_{12}H_{16}F_2N_5O_3^+$ $(M + H)^+$ 316.1216].

Preparation of 4



34 **4**

2-((3a*R*,4*R*,6*S*,6a*S*)-5,5-Difluoro-2,2-dimethyl-6-(6-(methylamino)-9*H*-purin-9-yl)tetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)ethan-1-ol (4). A steel pressure vessel containing a solution of **34** (10 mg, 0.03 mmol) in methanol (2 mL) was added 40% methylamine aqueous solution (0.25 mL, 3.22 mmol). The reaction mixture was heated at 50 °C for 5 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (methylene chloride:methanol = 9:1) to obtain **4** (0.008 g, 81%), which was crystallized from diethyl ether/methanol; white solid; mp 89-91 °C; $[\alpha]_D^{20}$ +2.0 (*c* 0.160, CH_3OH); UV (CH_3OH) λ_{max} 265 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.25 (s, 1H), 8.21 (s, 1H), 5.27 (ddd, J_1 = J_2 = 8.4, 17.8 Hz, 1H), 4.76 (dd, *J* = 6.6, 8.7 Hz, 1H), 4.06 (t, *J* =4.7 Hz, 1H), 3.74–3.68 (m, 2H), 3.11 (brs, 3H), 2.66–2.61 (m, 1H), 2.00–1.94 (m, 1H), 1.83–1.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 154.8, 151.5, 142.0, 126.1 (*J* = 250.1, 258.38 Hz), 121.2, 74.2 (*J* = 7.5 Hz), 73.0 (*J* = 7.0 Hz), 65.1 (*J* = 21.4 Hz), 61.3, 50.7, 31.3 (*J* = 6.5 Hz), 28.6; ^{19}F NMR (376 MHz, CD_3OD) δ −103.3, −115.9; HRMS (FAB) found 330.1386 [calcd for $C_{13}H_{18}F_2N_5O_3^+$ $(M+H)^+$ 330.1372].

V. References

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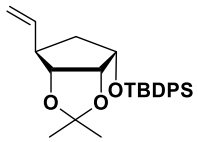
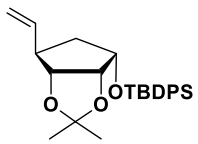
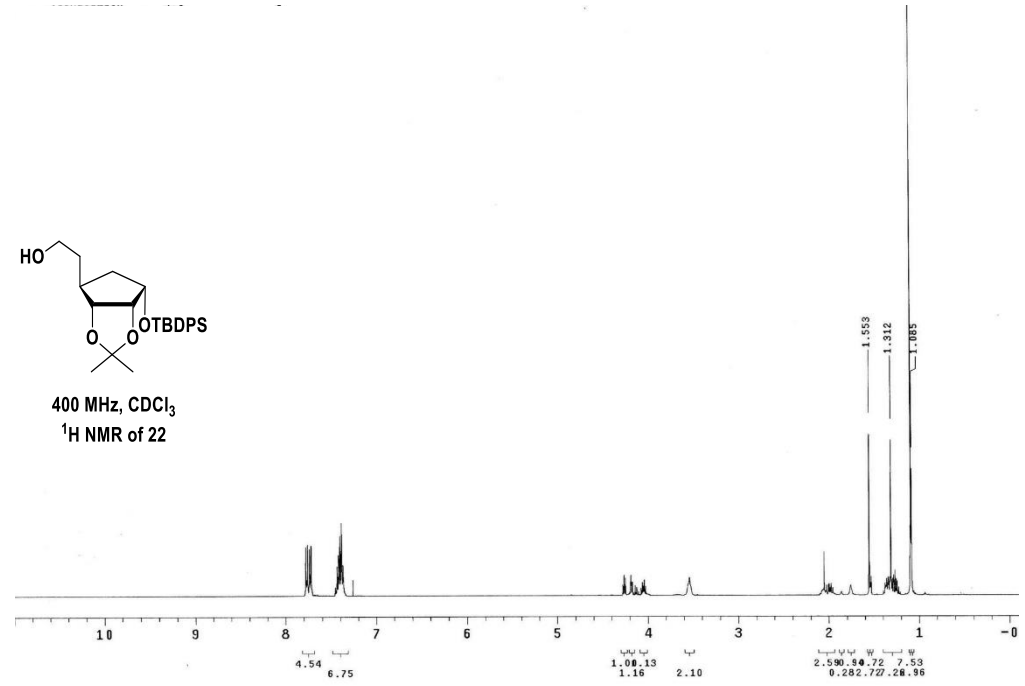
VI. ^{1}H and ^{13}C NMR Copies

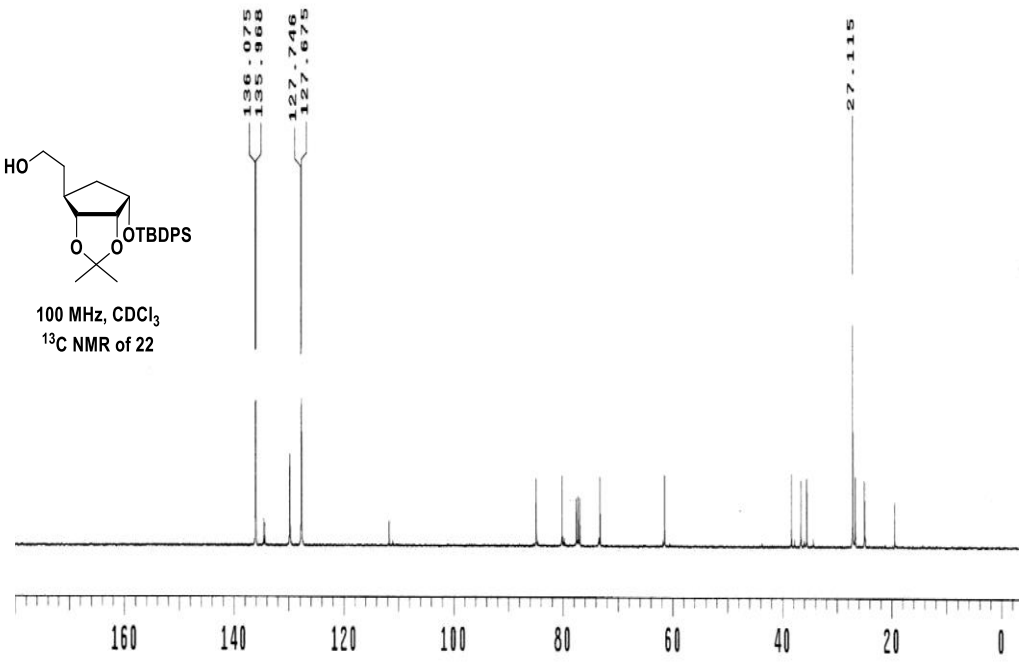


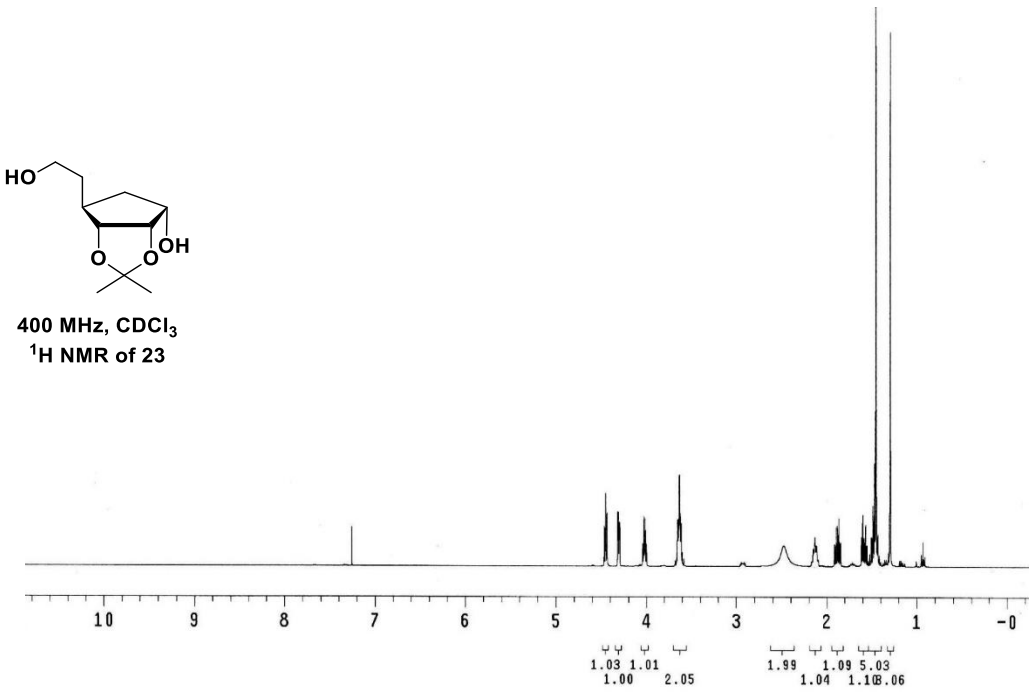
600 MHz, $CDCl_3$
^1H NMR of 21



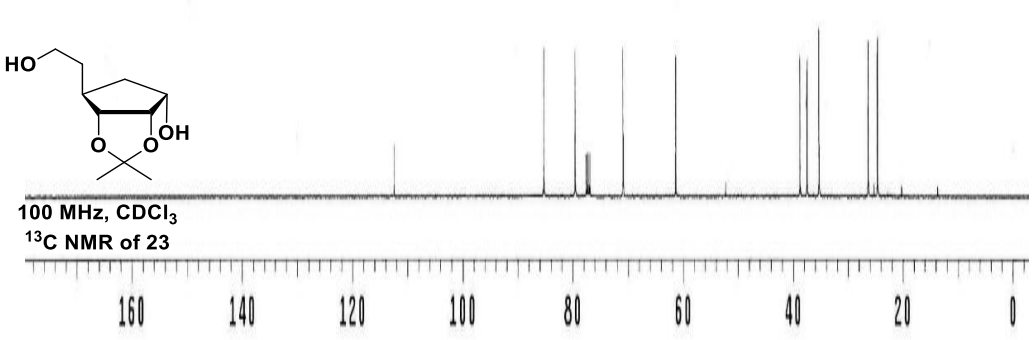
150 MHz, $CDCl_3$
^{13}C NMR of 21


HO
OTBDPS
O
O
400 MHz, CDCl3
1H NMR of 22
1.553
1.312
1.085
10
9
8
7
6
5
4
3
2
1
0
4.54
6.75
1.00
1.13
1.16
2.10
2.59
0.90
0.72
7.53
0.28
2.72
7.28
8.96

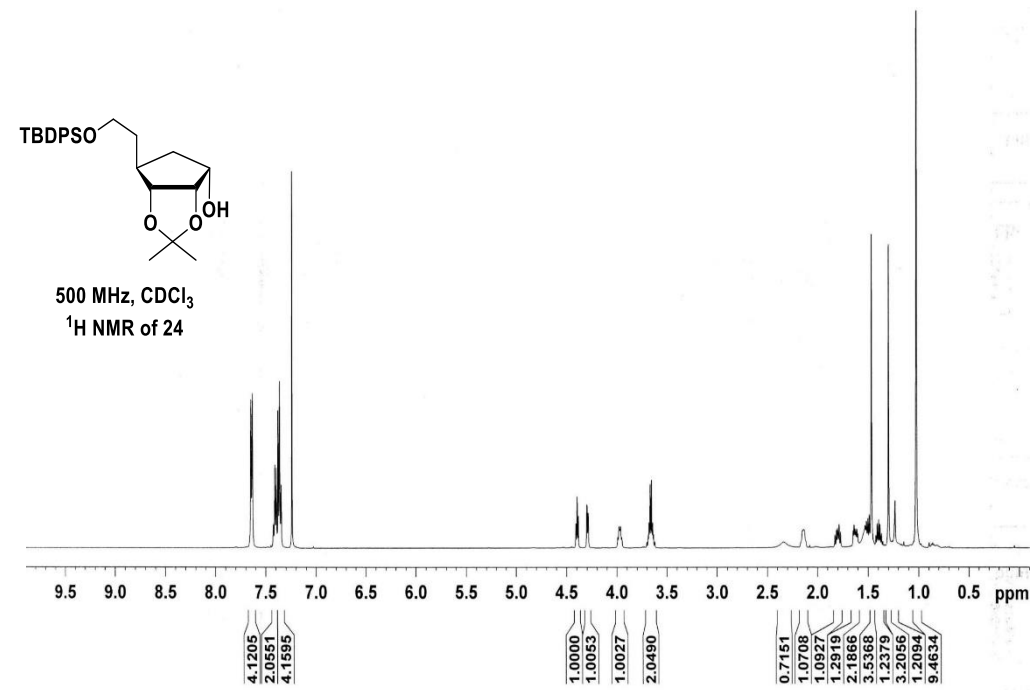

HO
OTBDPS
O
O
100 MHz, CDCl3
13C NMR of 22
136.075
135.968
127.746
127.675
27.115
160
140
120
100
80
60
40
20
0

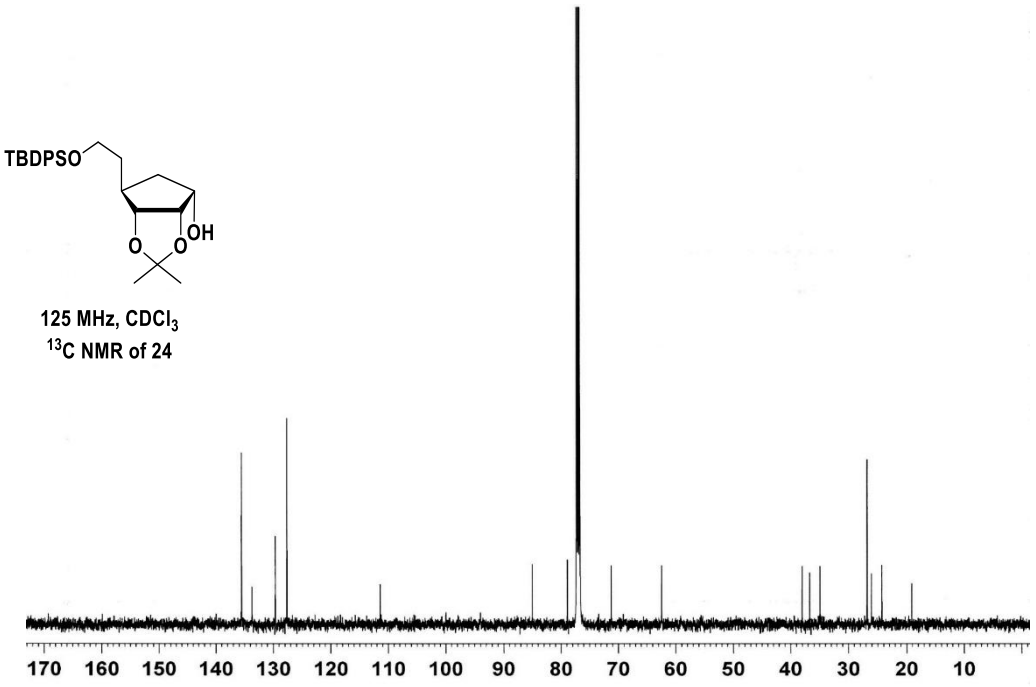


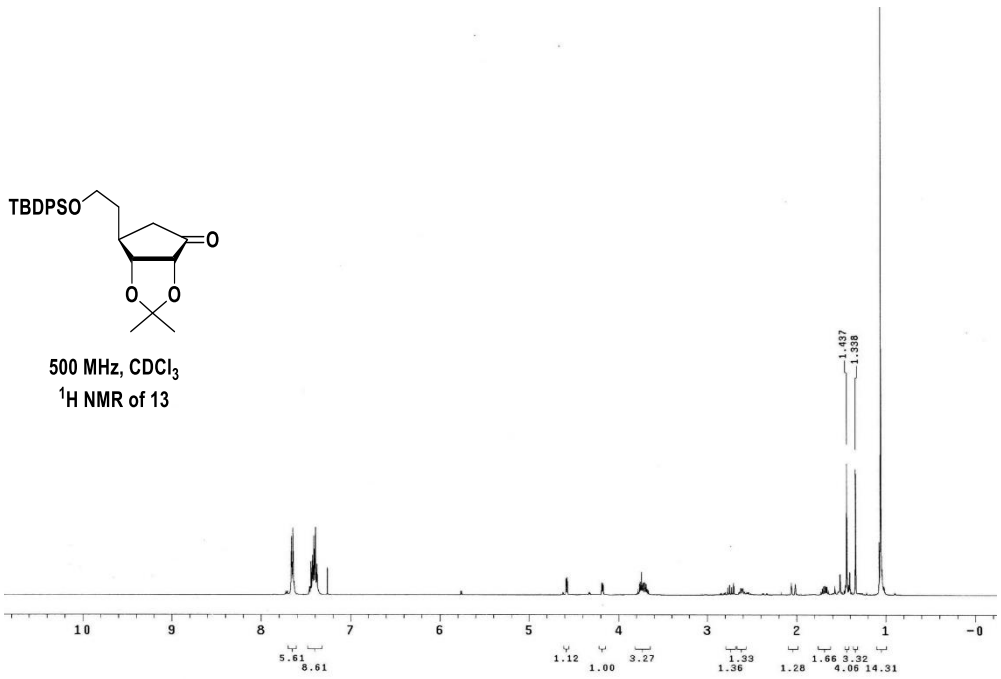
400 MHz, $CDCl_3$
^{1}H NMR of 23

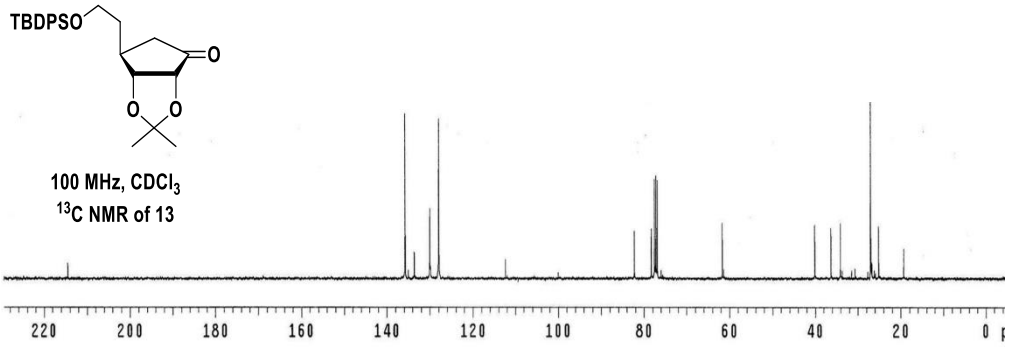


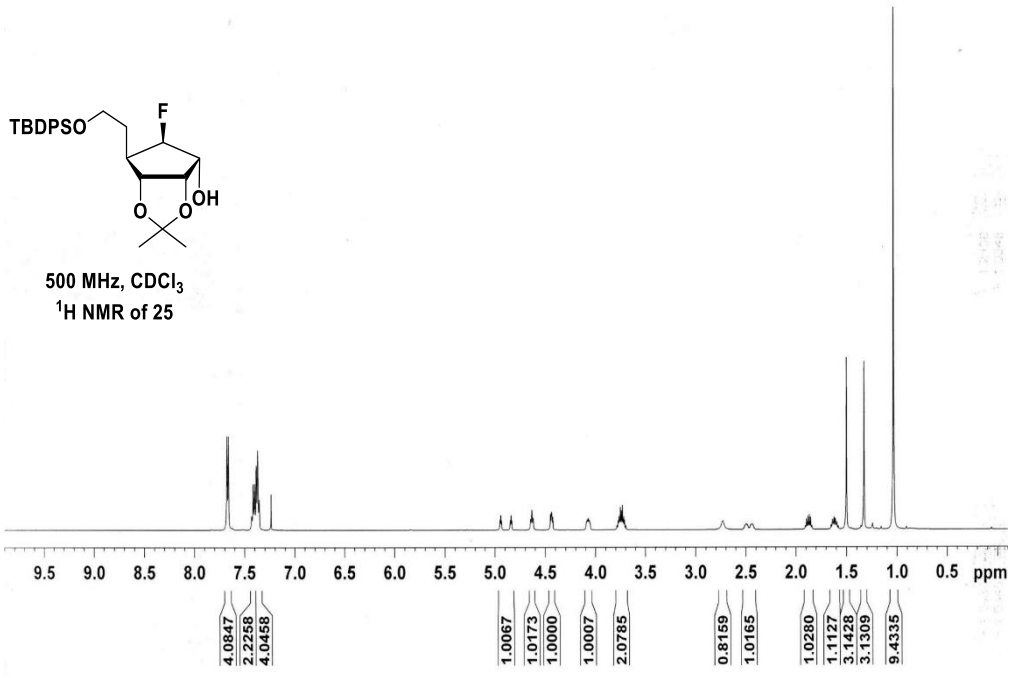
100 MHz, $CDCl_3$
^{13}C NMR of 23

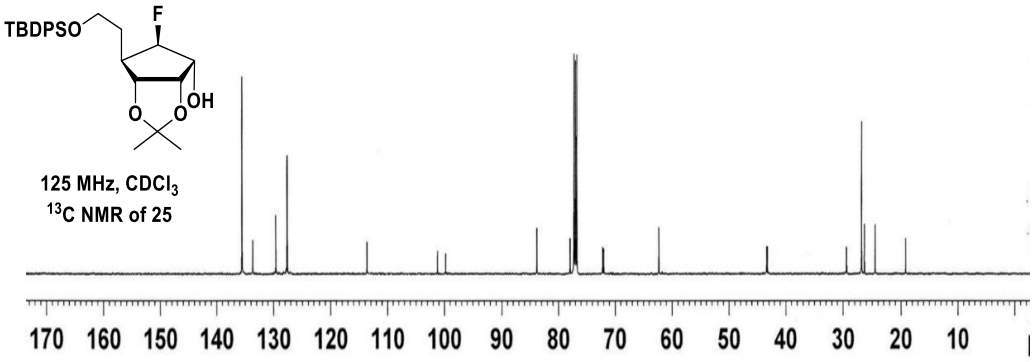

TBDPSO
O
O
OH
500 MHz, CDCl3
1H NMR of 24
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.1205
2.0551
4.1595
1.0000
1.0053
1.0027
2.0490
0.7151
1.0708
1.0927
1.2919
2.1866
3.5368
1.2379
3.2056
1.2094
9.4634

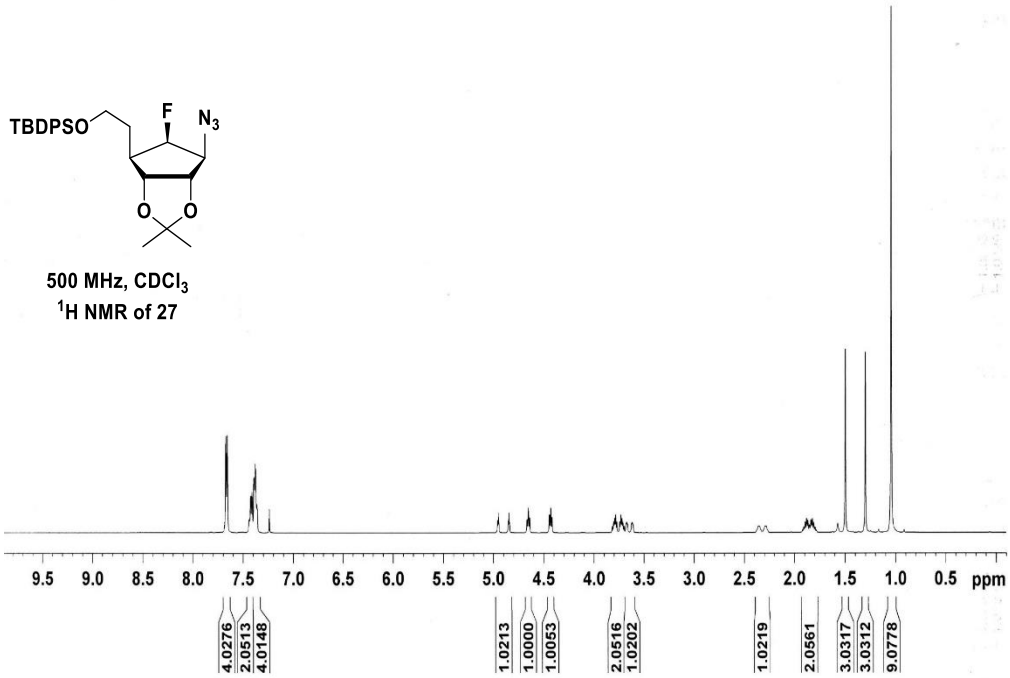

TBDPSO
O
O
OH
125 MHz, CDCl3
13C NMR of 24
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

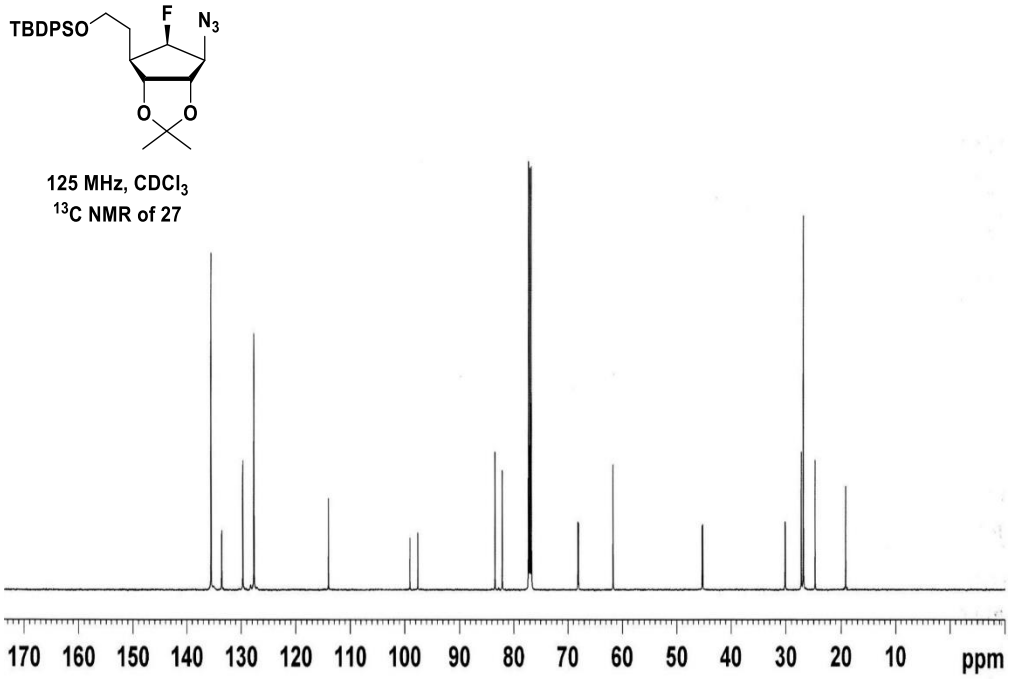

TBDPSO
O
O
O
500 MHz, CDCl3
1H NMR of 13
1.497
1.338
10
9
8
7
6
5
4
3
2
1
0
5.61
8.61
1.12
1.00
3.27
1.33
1.36
1.28
1.66
3.32
4.06
14.31

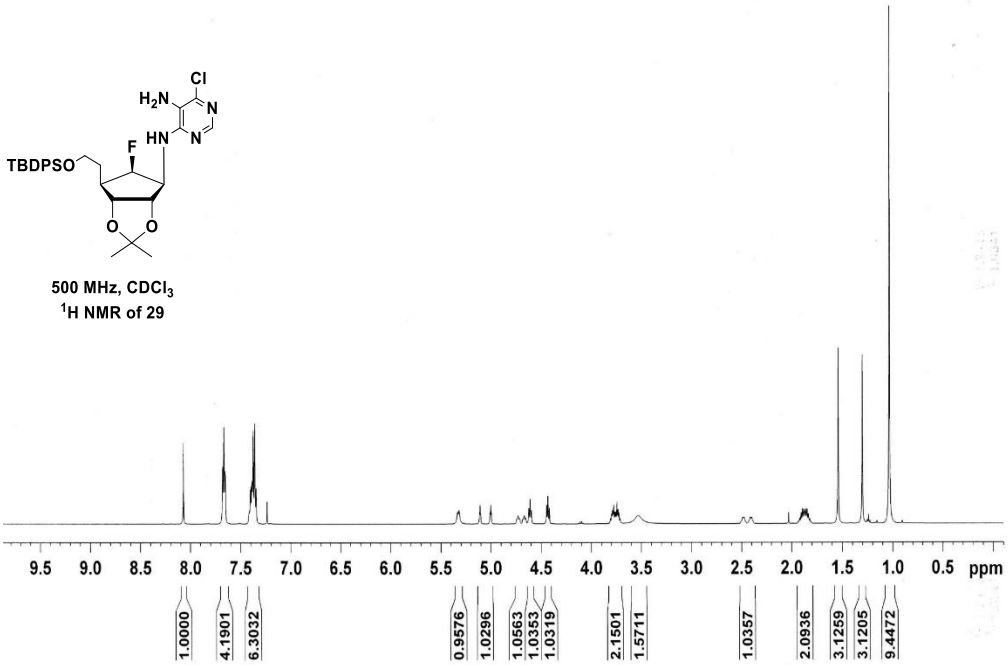

TBDPSO
O
O
O
100 MHz, CDCl3
13C NMR of 13
220
200
180
160
140
120
100
80
60
40
20
0


TBDPSO
F
O
O
OH
500 MHz, CDCl3
1H NMR of 25
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.0847
2.2258
4.0458
1.0067
1.0173
1.0000
1.0007
2.0785
0.8159
1.0165
1.0280
1.1127
3.1428
3.1309
9.4335

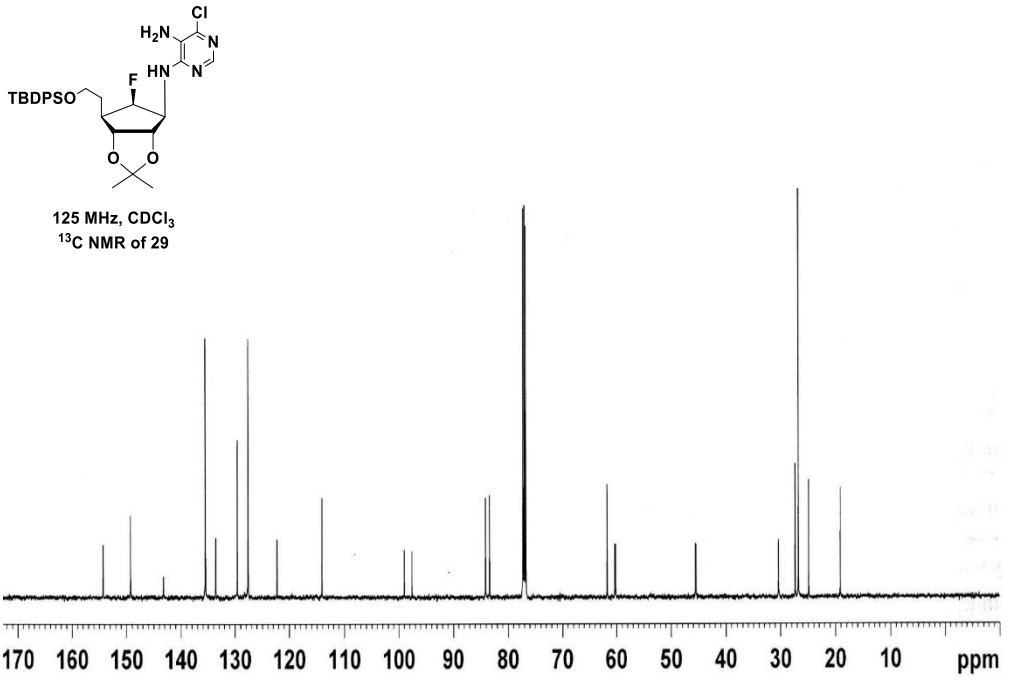

TBDPSO
F
O
O
OH
125 MHz, CDCl3
13C NMR of 25
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


TBDPSO
F
N3
O
O
500 MHz, CDCl3
1H NMR of 27
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.0276
2.0513
4.0148
1.0213
1.0000
1.0053
2.0516
1.0202
1.0219
2.0561
3.0317
3.0312
9.0778

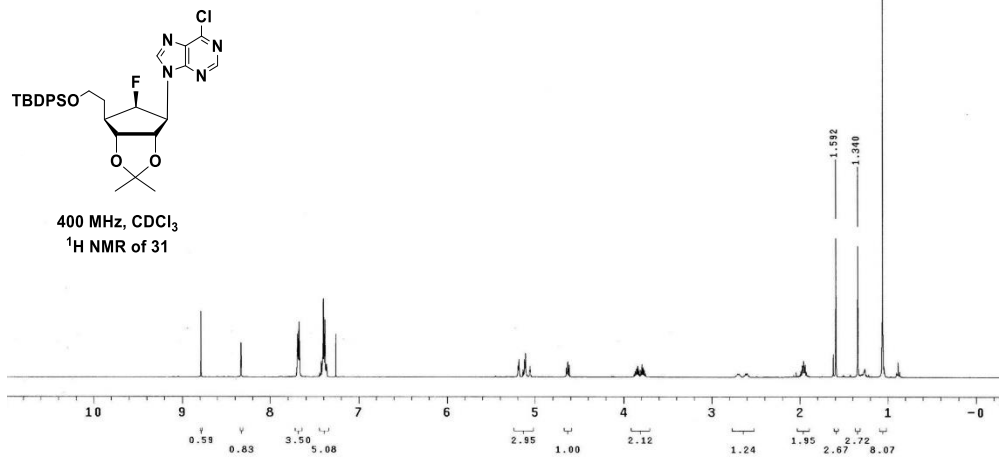

TBDPSO
F
N3
O
O
125 MHz, CDCl3
13C NMR of 27
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



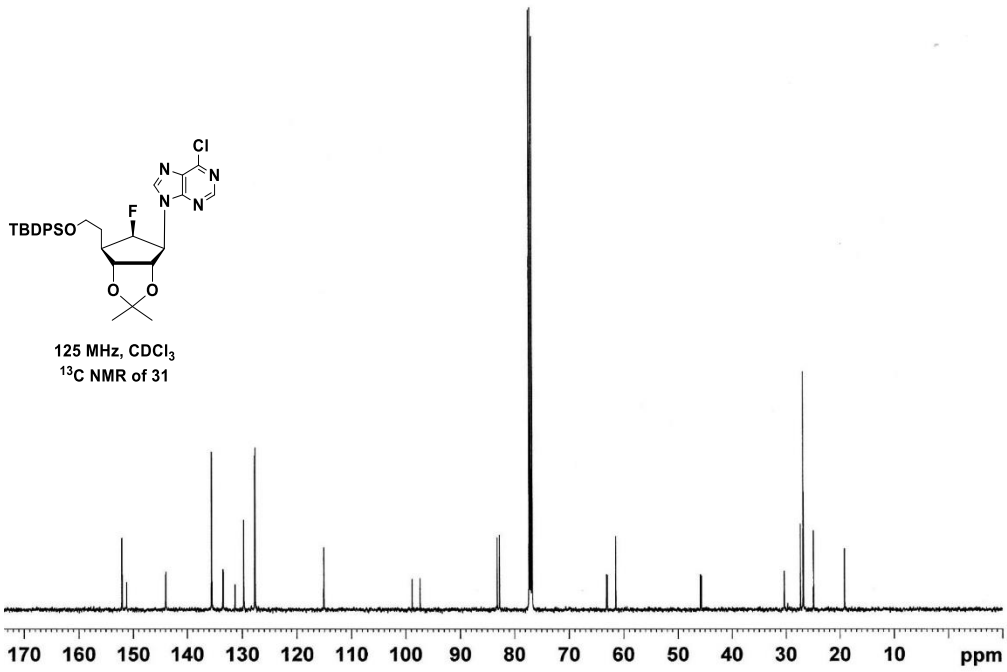
500 MHz, $CDCl_3$
^1H NMR of 29



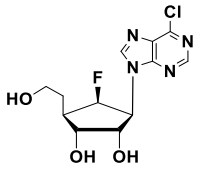
125 MHz, $CDCl_3$
^{13}C NMR of 29



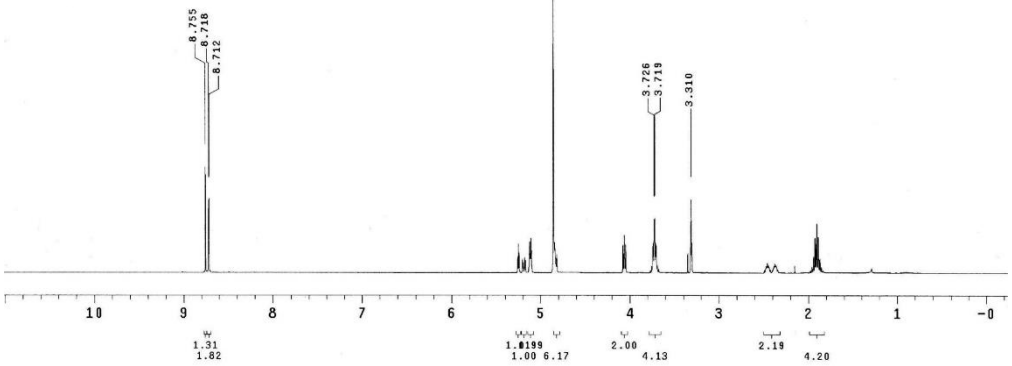
400 MHz, $CDCl_3$
^{1}H NMR of 31

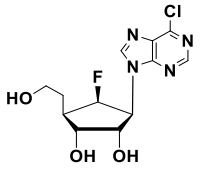


125 MHz, $CDCl_3$
^{13}C NMR of 31

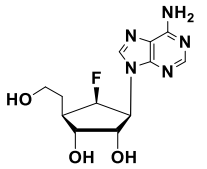


400 MHz, $CDCl_3$
^1H NMR of 33

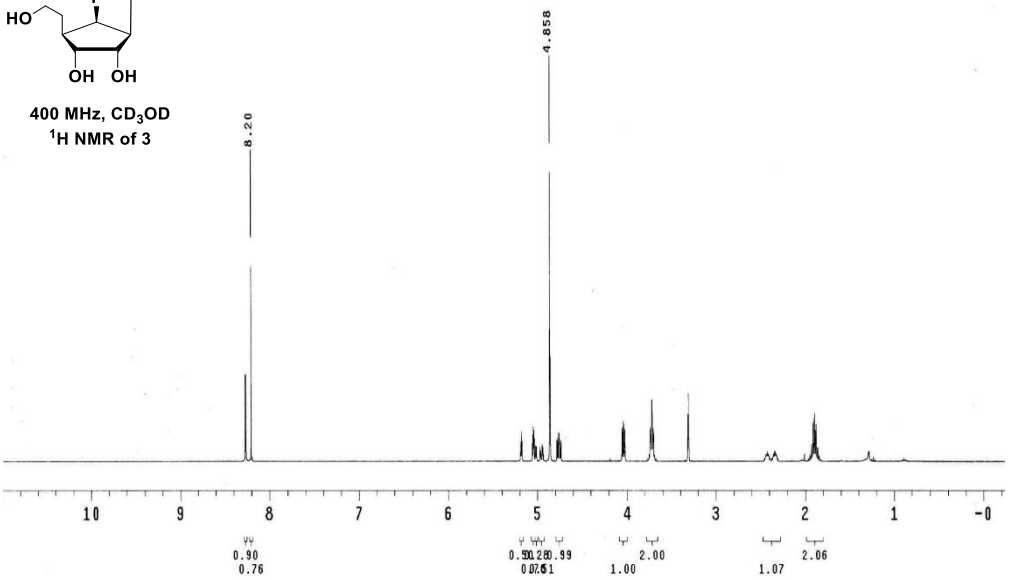


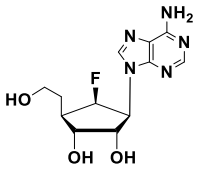


100 MHz, $CDCl_3$
^{13}C NMR of 33

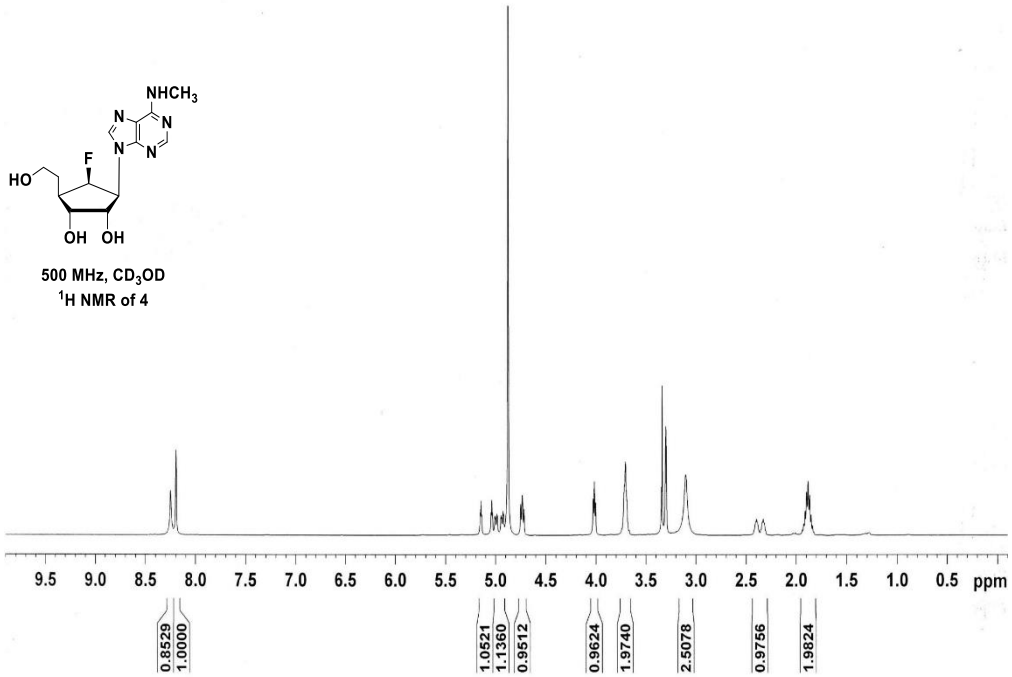


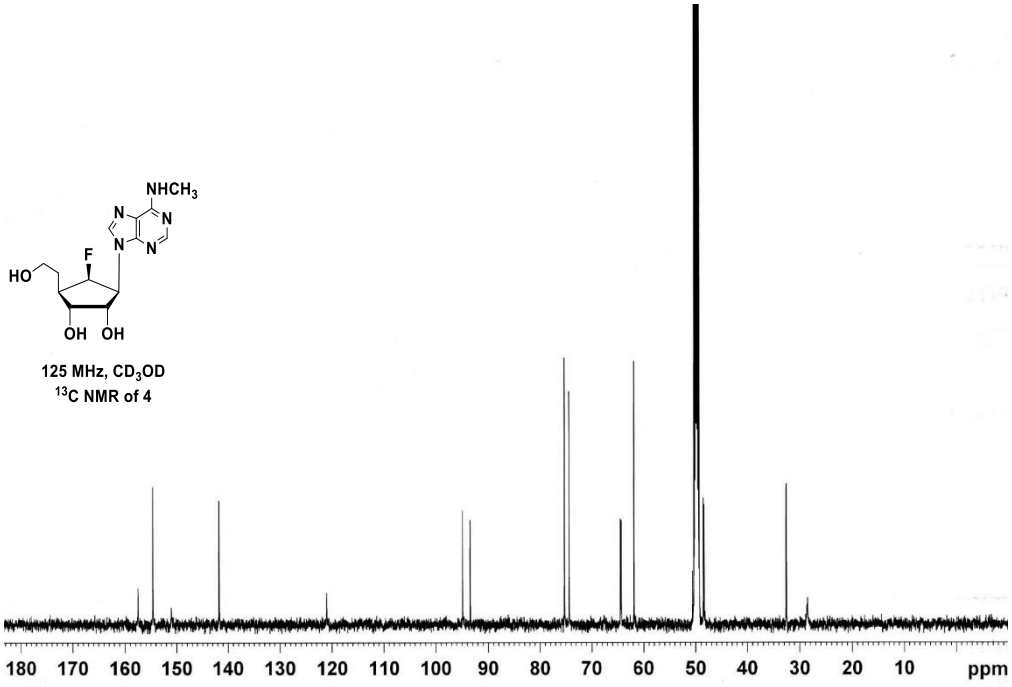
400 MHz, CD_3OD
^1H NMR of 3

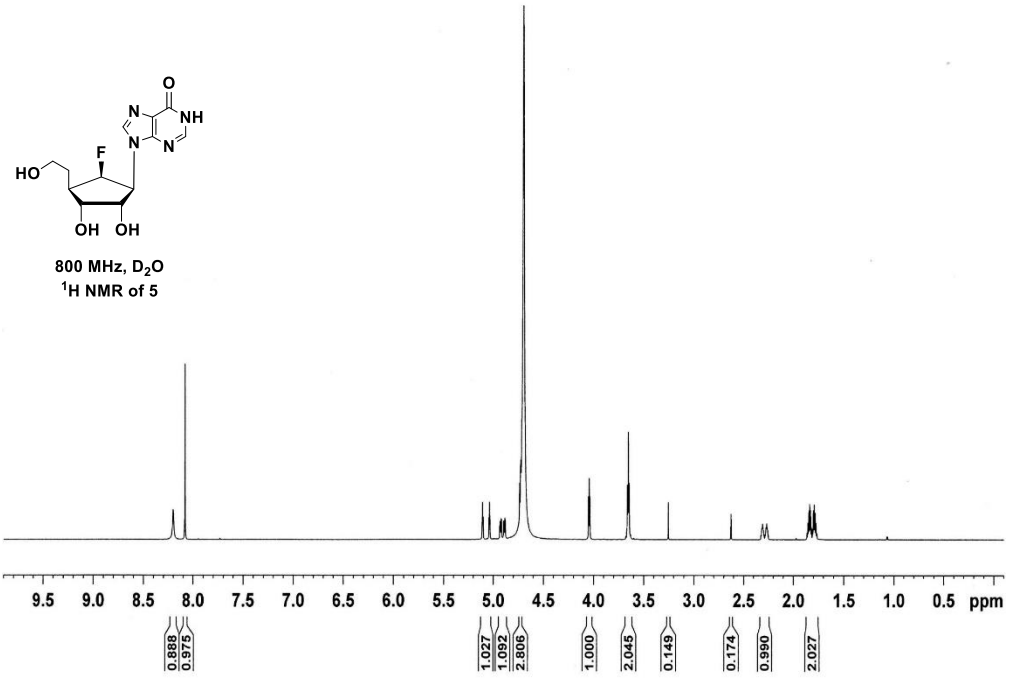


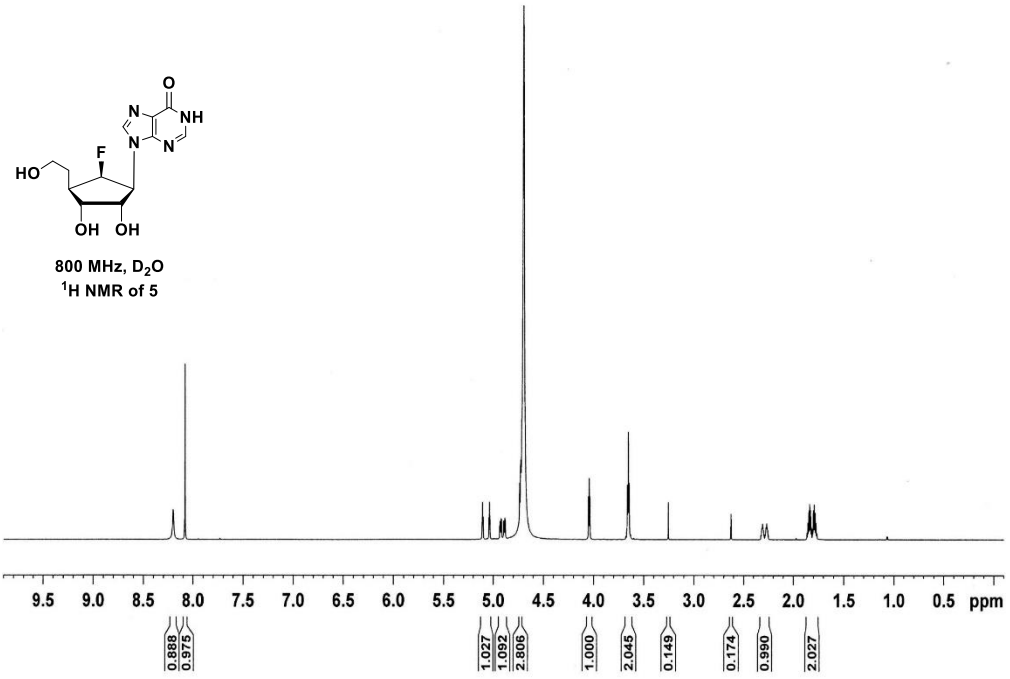


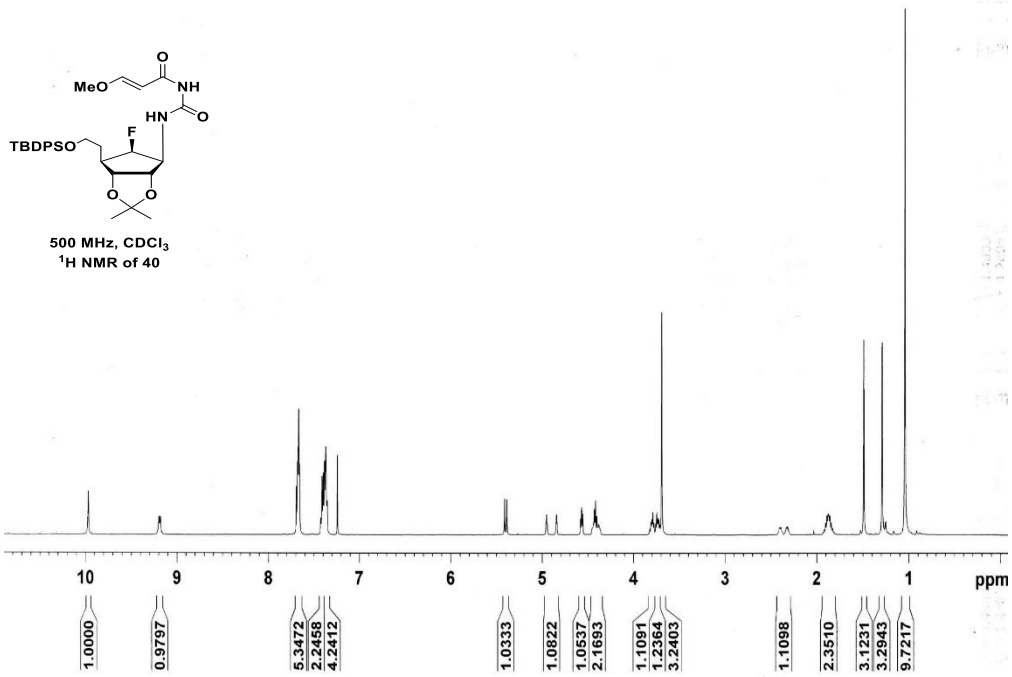
100 MHz, CD_3OD
^{13}C NMR of 3

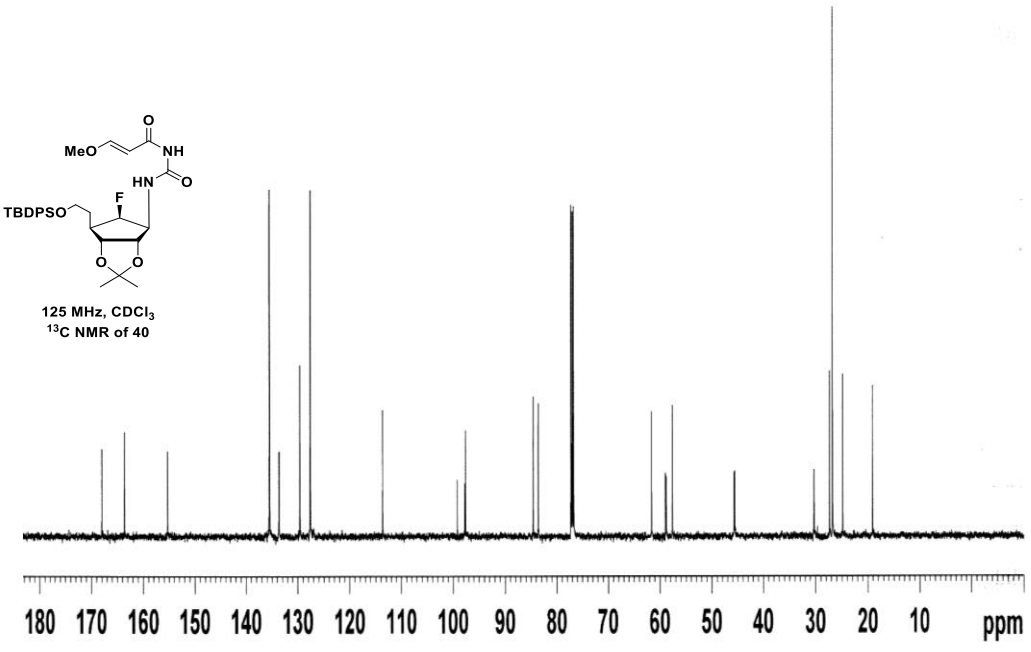

NHCH3
N
N
N
N
F
HO
OH OH
500 MHz, CD3OD
1H NMR of 4
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8529
1.0000
1.0521
1.1360
0.9512
0.9624
1.9740
2.5078
0.9756
1.9824

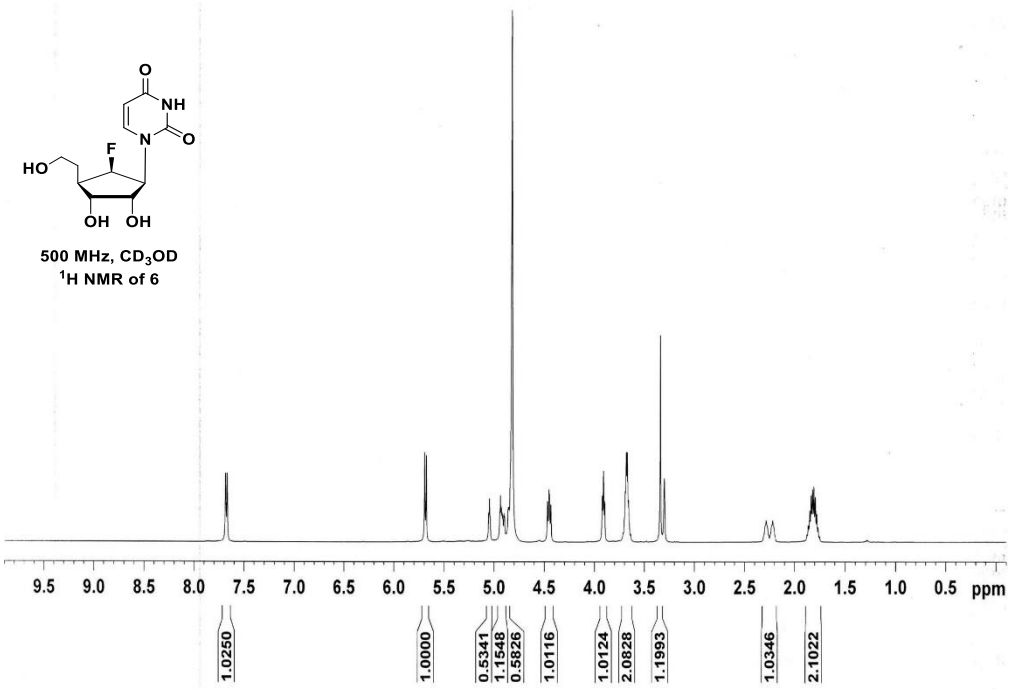

NHCH3
N
N
N
N
F
HO
OH OH
125 MHz, CD3OD
13C NMR of 4
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

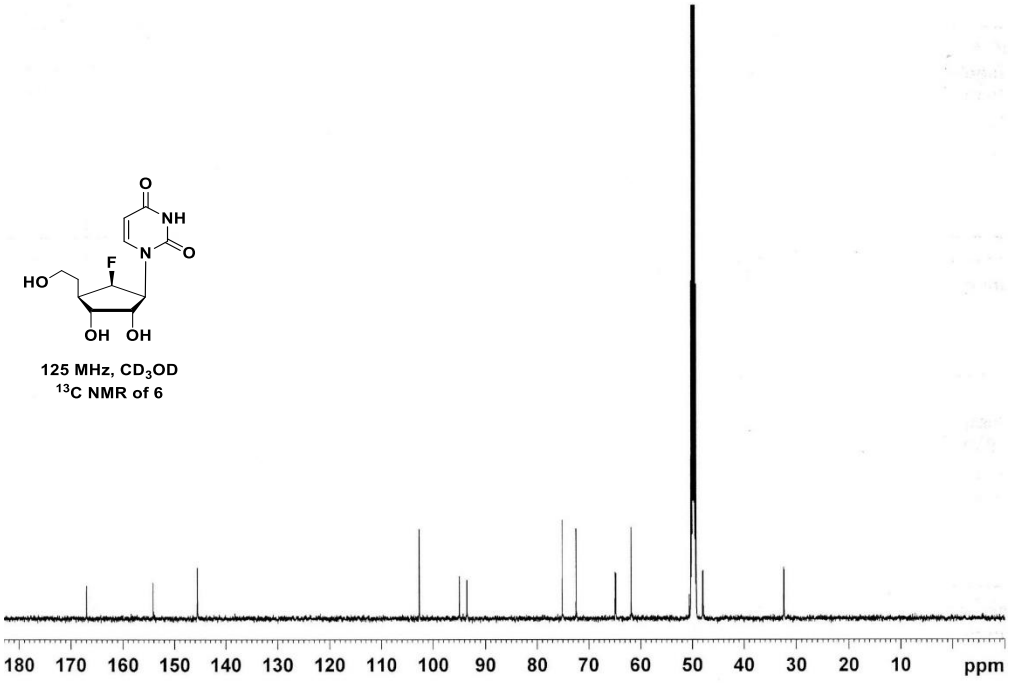

O
NH
N
N
N
F
HO
OH
OH
800 MHz, D2O
1H NMR of 5
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.888
0.975
1.027
1.092
2.806
1.000
2.045
0.149
0.174
0.990
2.027

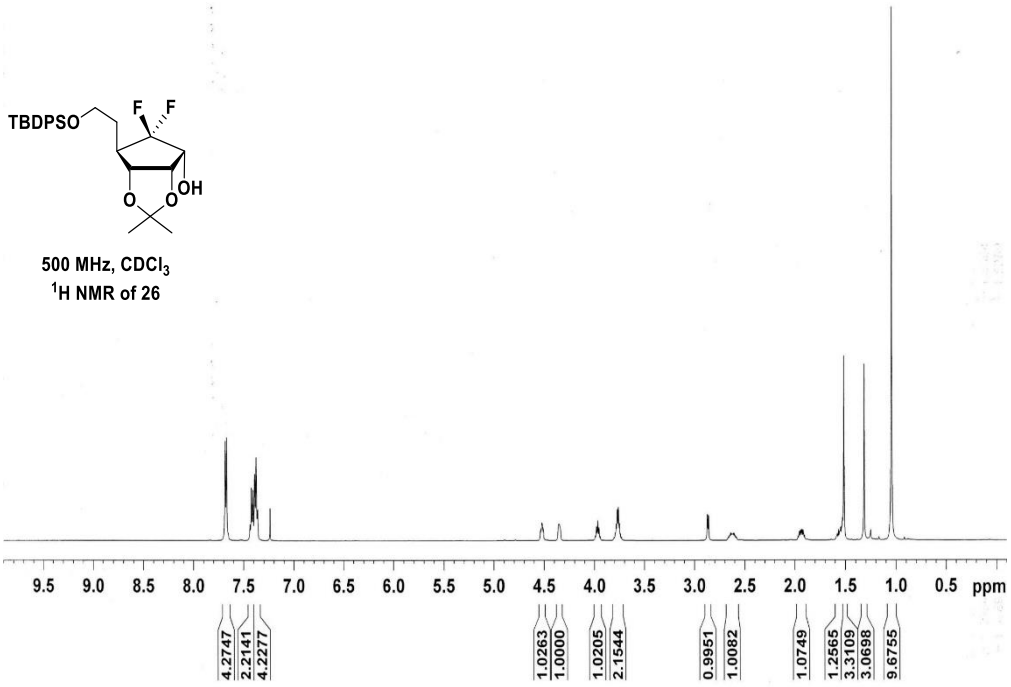

O
NH
N
N
N
F
HO
OH
OH
800 MHz, D2O
1H NMR of 5
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.888
0.975
1.027
1.092
2.806
1.000
2.045
0.149
0.174
0.990
2.027

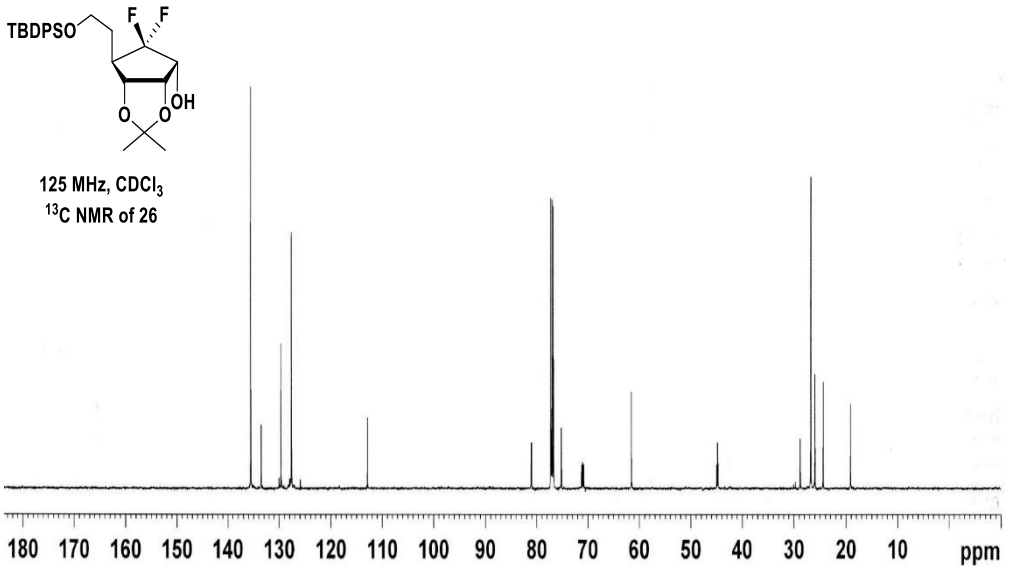

MeO
NH
HN
O
F
TBDPSO
O
O
500 MHz, CDCl3
1H NMR of 40
10
9
8
7
6
5
4
3
2
1
ppm
1.0000
0.9797
5.3472
2.2458
4.2412
1.0333
1.0822
1.0537
2.1693
1.1091
1.2364
3.2403
1.1098
2.3510
3.1231
3.2943
9.7217

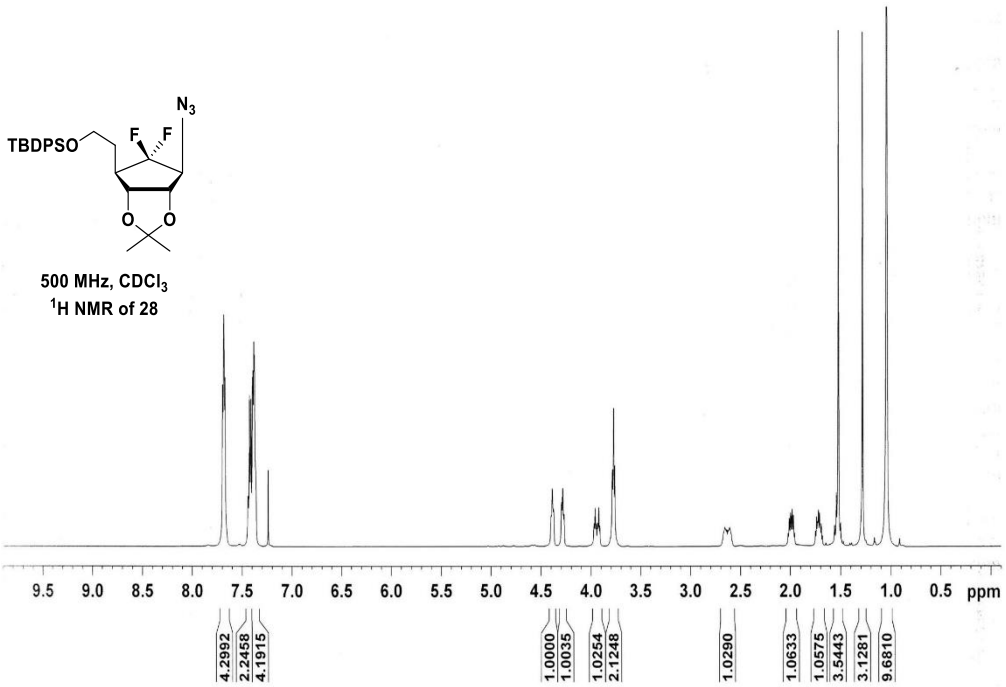

MeO
NH
HN
O
F
TBDPSO
O
O
125 MHz, CDCl3
13C NMR of 40
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

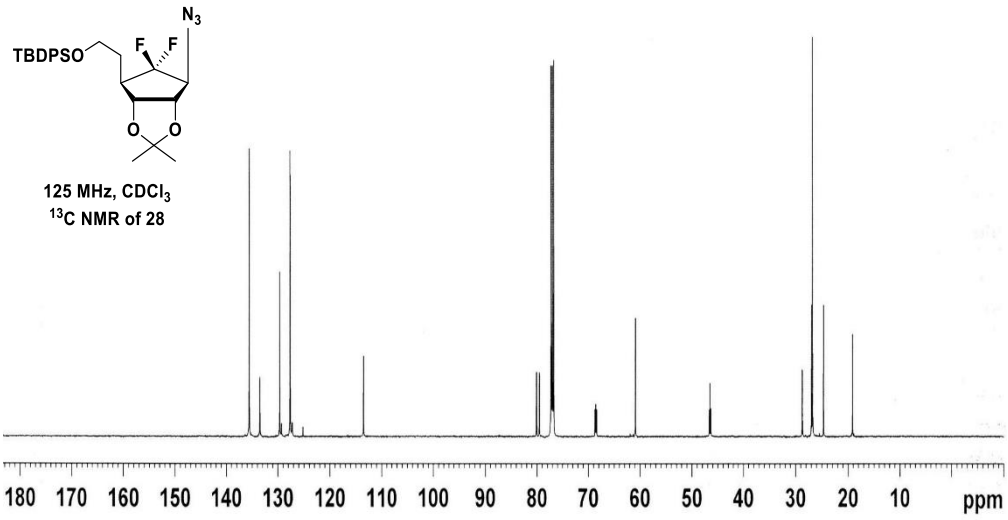

O
NH
N
O
F
HO
OH OH
500 MHz, CD3OD
1H NMR of 6
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0250
1.0000
0.5341
1.1548
0.5826
1.0116
1.0124
2.0828
1.1993
1.0346
2.1022

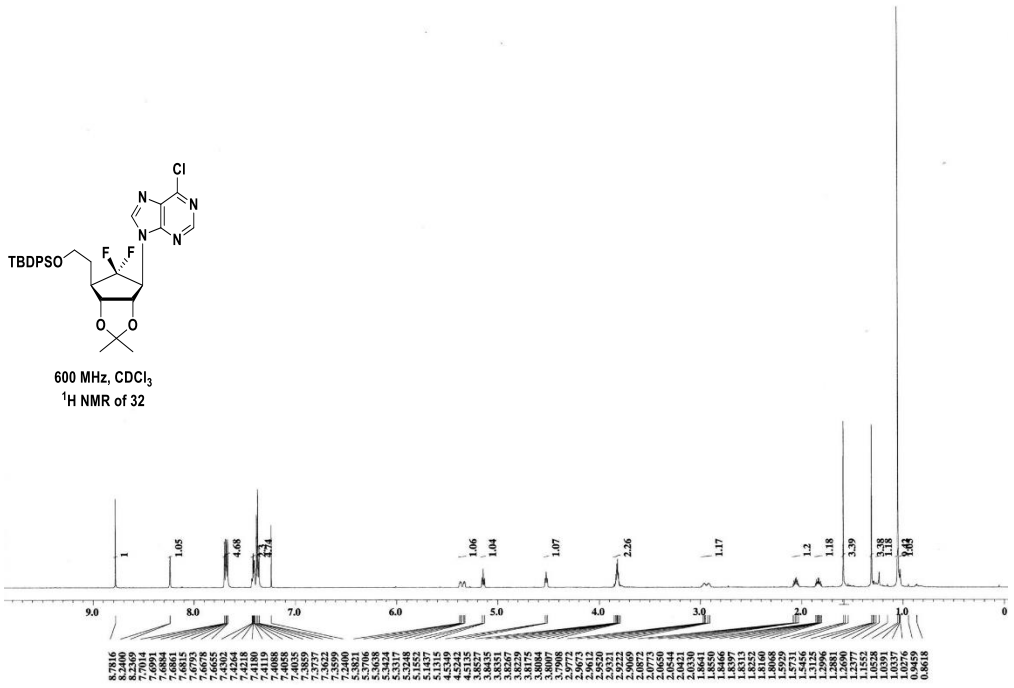

O
NH
N
O
F
HO
OH OH
125 MHz, CD3OD
13C NMR of 6
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

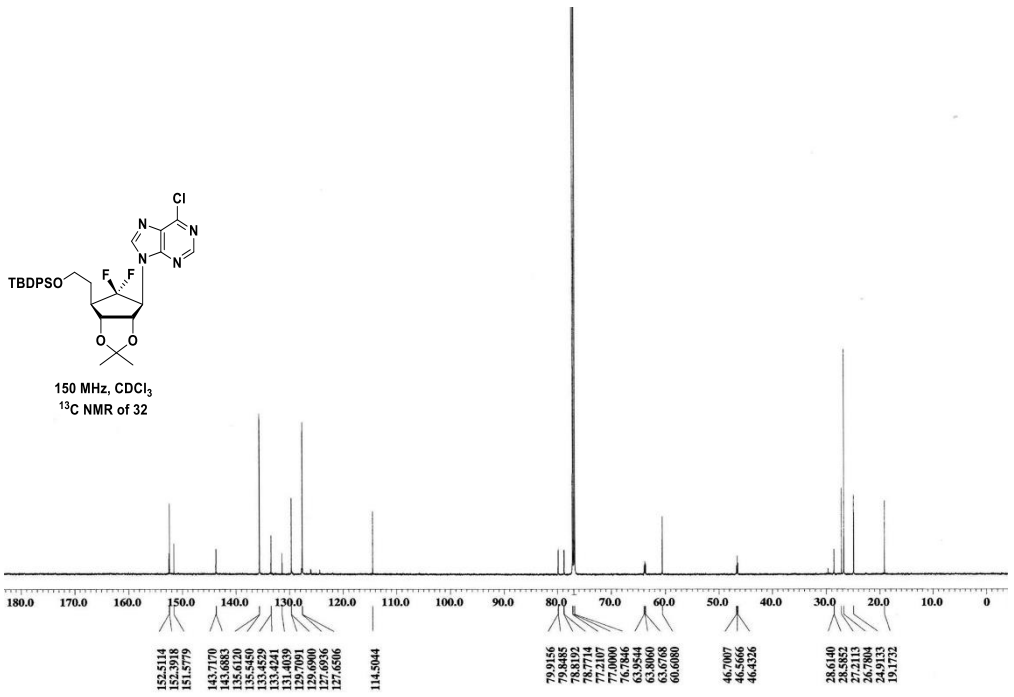

TBDPSO
F
F
O
O
OH
500 MHz, CDCl3
1H NMR of 26
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.2747
2.2141
4.2277
1.0263
1.0000
1.0205
2.1544
0.9951
1.0082
1.0749
1.2565
3.3109
3.0698
9.6755

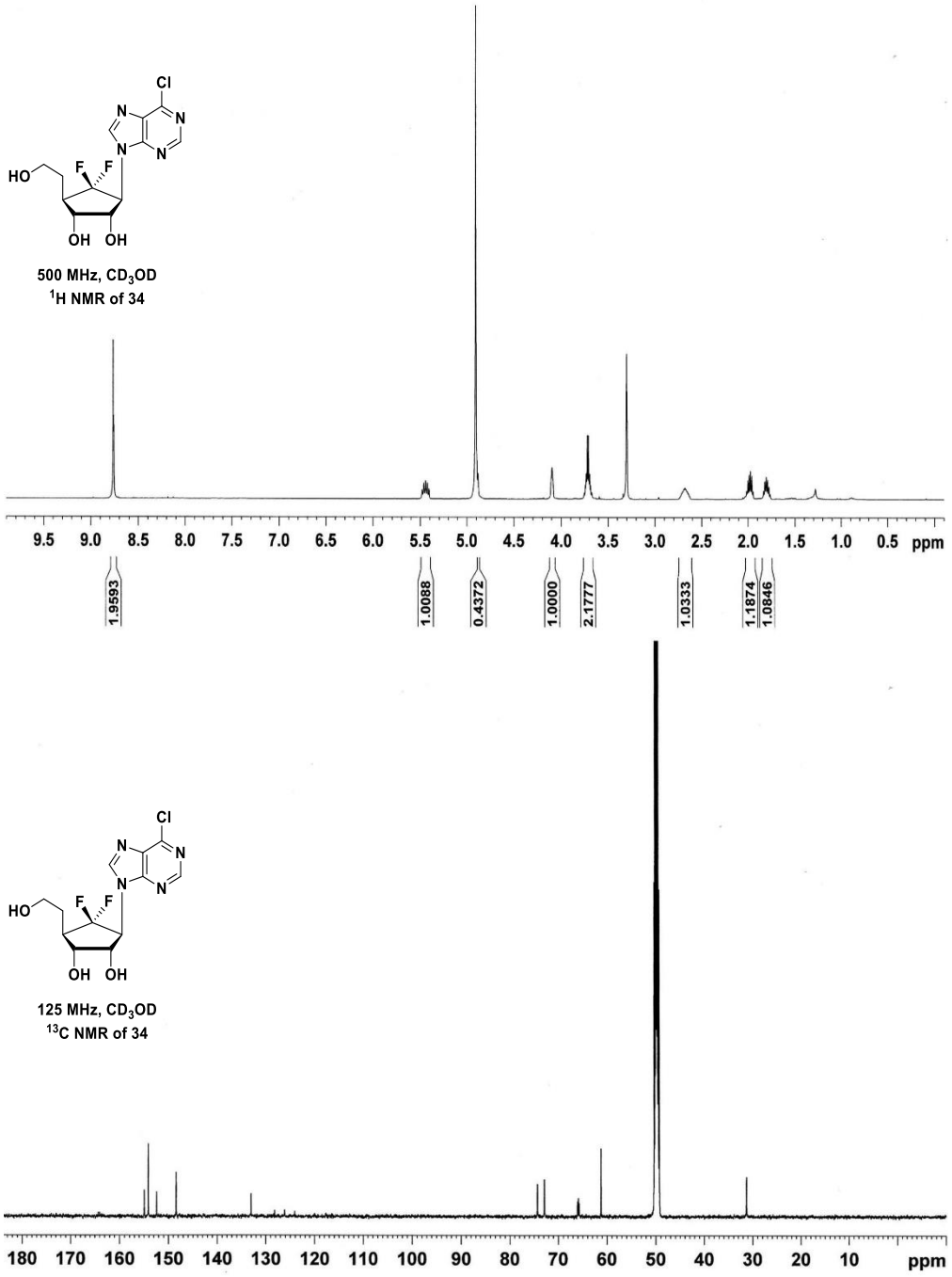

TBDPSO
F
F
O
O
OH
125 MHz, CDCl3
13C NMR of 26
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

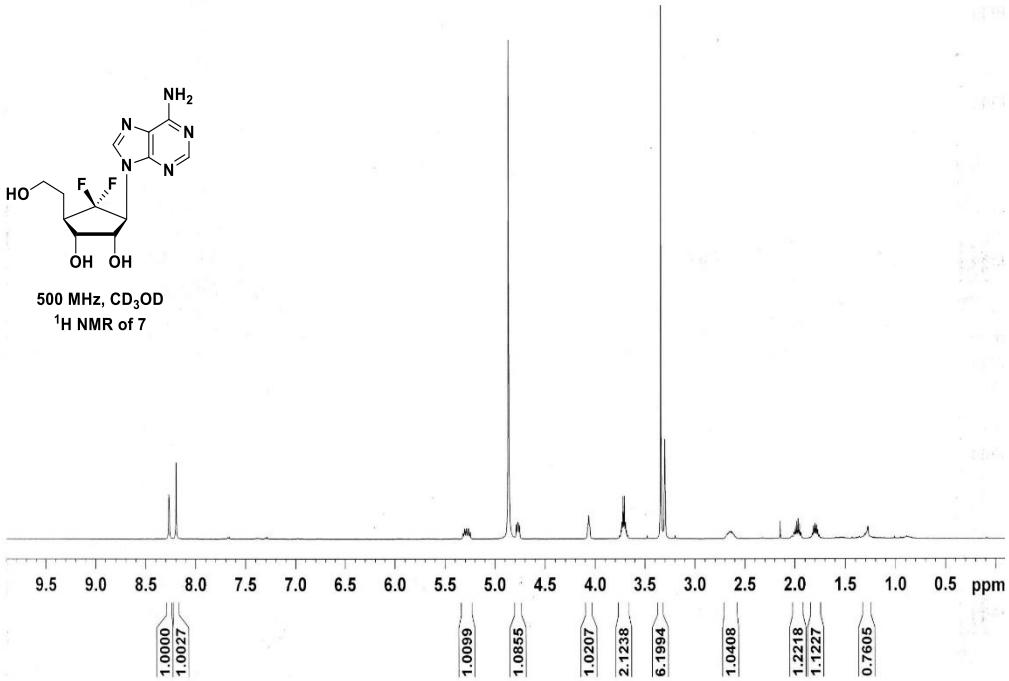

TBDPSO
N3
F
F
O
O
500 MHz, CDCl3
1H NMR of 28
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.2992
2.2458
4.1915
1.0000
1.0035
1.0254
2.1248
1.0290
1.0633
1.0575
3.5443
3.1281
9.6810

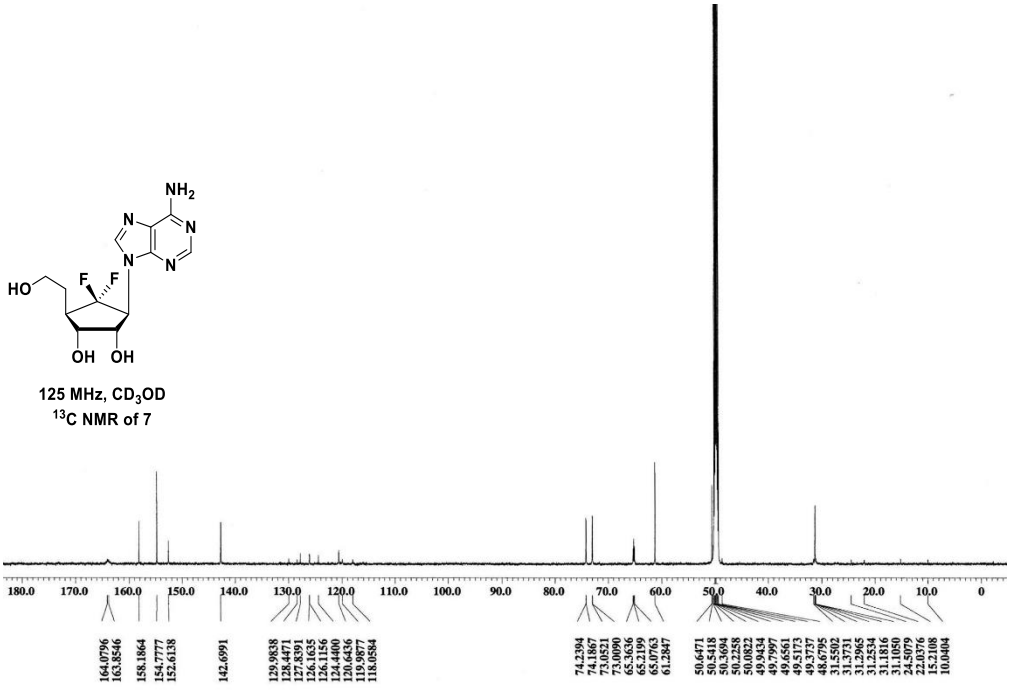

TBDPSO
N3
F
F
O
O
125 MHz, CDCl3
13C NMR of 28
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

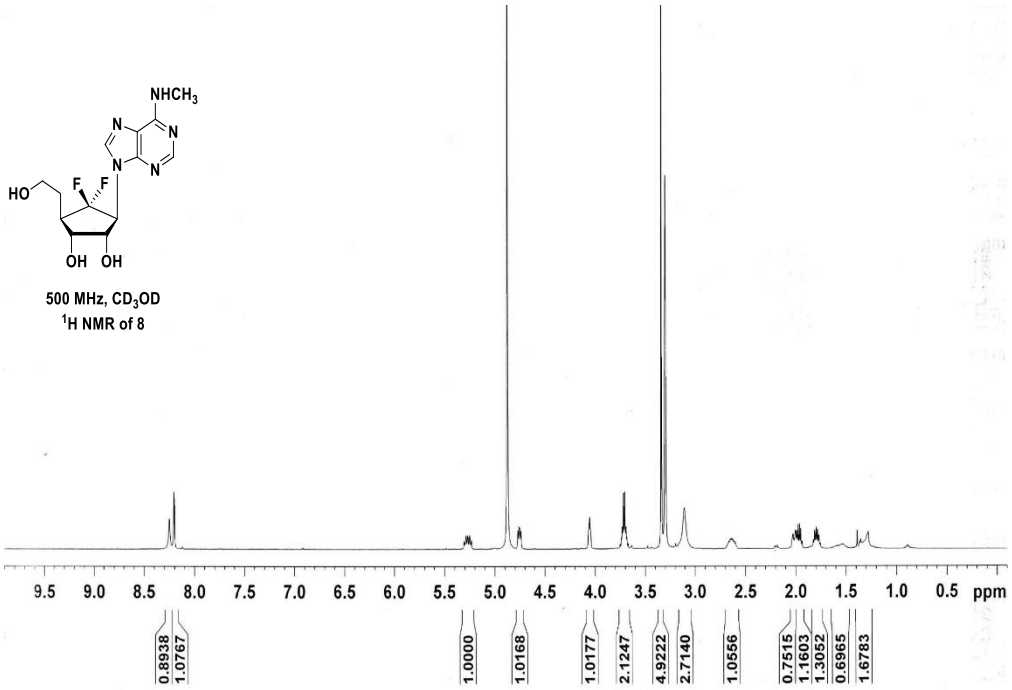

Cl
N
N
N
N
TBDPSO
F
F
O
O
600 MHz, CDCl3
1H NMR of 32

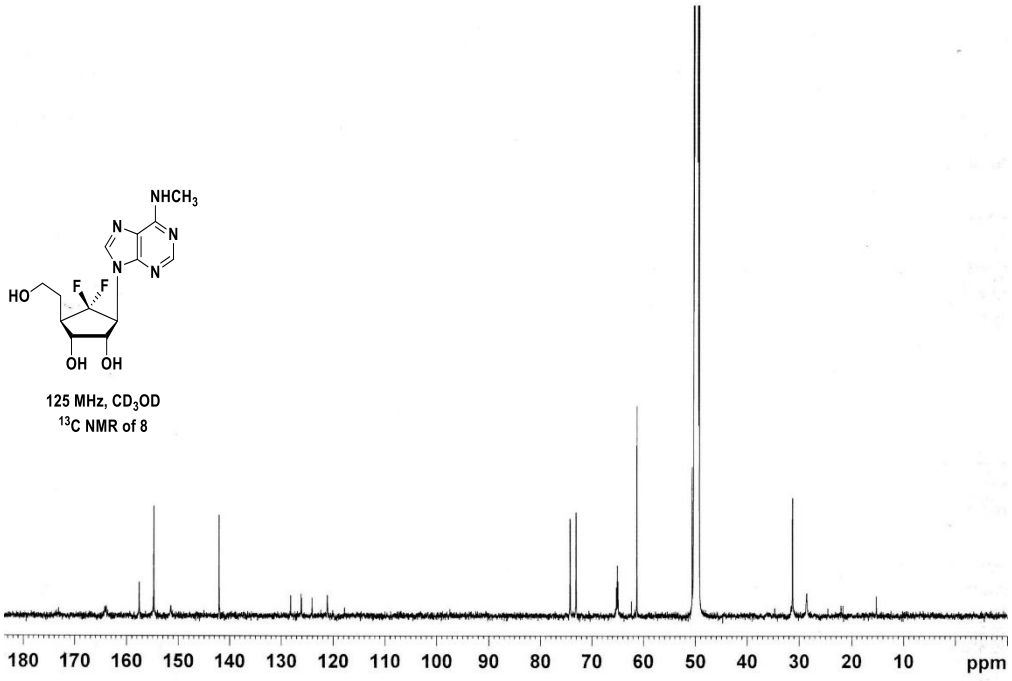

Cl
N
N
N
N
TBDPSO
F
F
O
O
150 MHz, CDCl3
13C NMR of 32


Cl
N
N
N
N
HO
F
F
OH
OH
500 MHz, CD3OD
1H NMR of 34
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.9593
1.0088
0.4372
1.0000
2.1777
1.0333
1.1874
1.0846
Cl
N
N
N
N
HO
F
F
OH
OH
125 MHz, CD3OD
13C NMR of 34
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


NH2
N
N
N
N
HO
F
F
OH
OH
500 MHz, CD3OD
1H NMR of 7
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
1.0027
1.0099
1.0855
1.0207
2.1238
6.1994
1.0408
1.2218
1.1227
0.7605


NH2
N
N
N
N
HO
F
F
OH
OH
125 MHz, CD3OD
13C NMR of 7
180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
164.0796
163.8546
158.1864
154.7777
152.6138
142.6991
129.9838
128.4471
127.4891
126.1635
126.1156
124.4400
120.6436
119.9877
118.0584
74.2394
74.1867
73.0521
73.0090
65.3636
65.2199
65.0763
61.2847
50.6471
50.5418
50.3694
50.2258
50.0823
49.9434
49.7997
49.6561
49.5173
49.3737
48.6795
31.5502
31.3781
31.2065
31.2534
31.1816
31.1050
24.5079
22.0376
15.2108
10.0404


NHCH3
N
N
N
N
HO
F
F
OH
OH
500 MHz, CD3OD
1H NMR of 8
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.8938
1.0767
1.0000
1.0168
1.0177
2.1247
4.9222
2.7140
1.0556
0.7515
1.1603
1.3052
0.6965
1.6783


NHCH3
N
N
N
N
HO
F
F
OH
OH
125 MHz, CD3OD
13C NMR of 8
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm